



Association of *JAK2V617F* allele burden and clinical correlates in polycythemia vera: a systematic review and meta-analysis

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Abstract

Janus kinase 2 (*JAK2*) V617F mutation is present in most patients with polycythemia vera (PV). One persistently puzzling aspect unresolved is the association between *JAK2V617F* allele burden (also known as variant allele frequency) and the relevant clinical characteristics. Numerous studies have reported associations between allele burden and both hematologic and clinical features. While there are strong indications linking high allele burden in PV patients with symptoms and clinical characteristics, not all associations are definitive, and disparate and contradictory findings have been reported. Hence, this study aimed to synthesize existing data from the literature to better understand the association between *JAK2V617F* allele burden and relevant clinical correlates. Out of the 1,851 studies identified, 39 studies provided evidence related to the association between *JAK2V617F* allele burden and clinical correlates, and 21 studies were included in meta-analyses. Meta-analyses of correlation demonstrated that leucocyte and erythrocyte counts were significantly and positively correlated with *JAK2V617F* allele burden, whereas platelet count was not. Meta-analyses of standardized mean difference demonstrated that leucocyte and hematocrit were significantly higher in patients with higher *JAK2V617F* allele burden, whereas platelet count was significantly lower. Meta-analyses of odds ratio demonstrated that patients who had higher *JAK2V617F* allele burden had a significantly greater odds ratio for developing pruritus, splenomegaly, thrombosis, myelofibrosis, and acute myeloid leukemia. Our study integrates data from approximately 5,462 patients, contributing insights into the association between *JAK2V617F* allele burden and various hematological parameters, symptomatic manifestations, and complications. However, varied methods of data presentation and statistical analyses prevented the execution of high-quality meta-analyses.

Keywords Polycythemia vera · Janus kinase 2 V617F · Allele burden · Variant allele frequency

Introduction

Polycythemia vera (PV), along with essential thrombocythemia and primary myelofibrosis, constitute the classic Philadelphia-negative myeloproliferative neoplasms (MPNs), a group of rare hematologic cancers characterized by the overproduction of one or more blood cell types. PV is typically marked by erythrocytosis, and in many cases concurrent leukocytosis and thrombocytosis. The excessive levels of blood cells result in blood thickening and a reduction in blood flow, elevating the risk of symptoms such as hemorrhage and thrombosis. These complications significantly impact the quality of life and in severe cases can be fatal. As early-stage patients are often asymptomatic for many years, and the symptoms of PV lack distinct features, suspicion of PV and subsequent diagnosis frequently occur later, following the exclusion of other diseases.

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In 2005, several research groups independently identified a mutation in the Janus kinase 2 (*JAK2*) gene, *JAK2V617F*, that revolutionized the diagnosis and treatment of MPNs [1–4]. *JAK2*, a member of the Janus family of nonreceptor tyrosine kinases, plays a crucial role in hematopoiesis. Upon binding to associated receptor molecules, *JAK2* induces conformational changes that phosphorylate specific tyrosine residues on the intracellular domain of the receptor, creating docking sites for specific signaling molecules [5]. The *JAK2V617F* mutation removes the intrinsic inhibitory mechanism and results in the overactivation of the *JAK2* protein. This leads to constitutional activation of its receptors, aberrant downstream signaling, and an increase in hematopoiesis [6]. This mutation is present in 95% of patients with PV and 50–60% of patients with essential thrombocythemia or primary myelofibrosis [7]. The remaining PV patients without the mutation often harbor other mutations located on exon 12 of *JAK2* [8]. Therefore, the involvement of *JAK2* mutations in PV underpins its significance in this disease.

One persistently puzzling aspect in PV that remains somewhat unresolved is the association between *JAK2V617F* allele burden (or variant allele frequency) and the relevant clinical characteristics. Numerous studies have reported associations between allele burden and both hematologic and clinical features of MPNs. For instance, a high allele burden has been correlated with increases in thrombosis and disease transformation [9]. While there are strong indications linking high allele burden in PV patients with symptoms and clinical characteristics, not all associations are definitive, and disparate and contradictory findings have been reported. To the best of our knowledge, a meta-analysis has yet to be conducted to investigate the association between *JAK2V617F* allele burden and the clinical characteristics of PV. Hence, this study aimed to synthesize existing data from the literature to better understand the association between *JAK2V617F* allele burden and relevant clinical correlates.

Methods

Eligibility criteria, information sources and search strategy

This systematic review and meta-analysis study adhered to the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines [10]. This review included studies published between January 1st, 2005, and February 28th, 2022, where patients were diagnosed with PV, *JAK2V617F* allele burden was quantified, and

hematologic parameters and/or clinical outcomes were measured. Only original research articles were considered.

This systematic review was conducted across three databases, namely PubMed, Science Direct, and Wiley Online Library. The following search terms were utilized: (“*JAK2*” OR “*JAK2V617F*” OR “*V617F*”) AND (“allele burden” OR “allelic burden” OR “clonal dominance” OR “variant allele frequency”) AND (“Polycythemia” OR “Polycythemia”). Exclusion criteria encompassed studies not published in English, those lacking full-text, duplicate studies, and reviews.

Selection process and data collection process

Two authors (JLC & AJL) independently screened the title and abstract of each study for initial inclusion in our systematic review. Studies upon which both authors reached consensus were included. Any disagreements were resolved through discussion or by a third author if necessary. Two authors independently reviewed the full text (JLC & LHY) for data applicability.

Only studies presenting data pertaining to a hematologic parameter or clinical outcome correlating with a quantified *JAK2V617F* allele burden were included. Discrepancies were resolved through discussion or by a third author if necessary. Both title and abstract screening as well as full-text review were conducted on the Covidence platform (app.covidence.org). Data extraction was performed using a standardized form in Microsoft Excel by one author (JLC), with the accuracy of the extracted data verified by two authors (CCC & HHA).

Data items

Peripheral blood or bone marrow samples from patients were taken at the time of diagnosis or during follow-up. Some patients were on treatments for PV, which included aspirin, phlebotomy, and/or cytoreductive agents. *JAK2* allele burden was measured using validated methods. Various clinical outcomes and hematologic parameters were assessed. Continuous variables extracted included red blood cell count (RBC), platelet count (PLT), white blood cell count (WBC), hematocrit (Hct), hemoglobin (Hb), spleen size, and *JAK2V617F* allele burden. Count variables extracted included splenomegaly, pruritus, thrombosis, hemorrhage, post-PV transformation to myelofibrosis (MF), and post-PV transformation to acute myeloid leukemia (AML). The mean and standard deviation of the continuous variables were extracted. Correlation coefficients and sample sizes were extracted where Pearson or Spearman correlation tests were performed. The following information was also extracted: surname of first author, year of

publication, country of study site, sample size, source of DNA, *JAK2V617F* quantification method, sample collection time point, *JAK2V617F* allele burden data presentation, and applied statistical methods.

Study risk of bias assessment

Two authors (JLC & LHY) independently evaluated the quality of studies using critical appraisal checklists from the Joanna Briggs Institute (JBI) [11]. The criteria included the following items: (1) Were the criteria for inclusion in the sample clearly defined?; (2) Were the study subjects and the setting described in detail?; (3) Was the exposure measured in a valid and reliable way?; (4) Were objective, standard criteria used for measurement of the condition?; (5) Were confounding factors identified?; (6) Were strategies to deal with confounding factors stated?; (7) Were the outcomes measured in a valid and reliable way?; and (8) Was appropriate statistical analysis used?. Each item received a response of “Yes,” “No,” or “Unclear,” corresponding to 1, 0, or 0 points, respectively. Studies consistent between the two authors with fewer than three items marked as “No” or “Unclear” were included in the systematic review and meta-analysis. Disagreements between authors were resolved through discussion or by involving a third author if needed.

Effect measures and synthesis methods

Qualitative descriptions and summaries of evidence were provided, and meta-analyses were conducted using Comprehensive Meta-Analysis 3.0. Pooled odds ratio (OR), standardized mean difference (SMD), correlation coefficients, 95% confidence intervals (95%CI), and standard error (SE) were calculated using the software.

Due to the diversity of the included data, we categorized them based on how *JAK2V617F* allele burden was presented: (a) *JAK2V617F* allele burden tested against another variable using correlation tests; (b) patients grouped by *JAK2V617F* allele burden level, with mean values and standard deviations of their clinical characteristics presented; or (c) patients grouped by *JAK2V617F* allele burden level, with count data presented for their clinical measurements (e.g. record of later MF transformation). For uniformity, continuous variables were converted into the same units (e.g. $10^9/\text{ml}$).

All included studies following full-text review were tabulated (Table 1). Meta-analyses were depicted as forest plots (Figs. 2, 3 and 4). Random effects models were employed to address heterogeneity in all meta-analyses.

Mixed effects models were used for subgroup analyses where applicable. Measures of heterogeneity, including Cochran’s Q , I^2 , and Tau^2 , were reported. Sensitivity

meta-analyses were not conducted due to the limited number of publications. In cases where mean and standard deviation were unavailable, the range rule was applied for estimation.

Results

Study selection, study characteristics, and risk of bias in studies

A flow diagram illustrating the screening process is presented in Fig. 1. Initially, 1,851 studies were identified. After removing duplicates and non-original articles, 985 studies remained. Following title and abstract screening, 120 studies were considered for full-text review. After reviewing the full text, 39 studies [9, 12–49] provided evidence related to the association between *JAK2V617F* allele burden and clinical correlates (Table 1). Details on the excluded 74 records (1 duplicate) [50–122] are presented in Supplemental Information 1.

A total of 21 studies were included in meta-analyses, spanning the years 2006 to 2021 and originating from 12 countries (Belgium, China, Denmark, France, Iran, Italy, Japan, Korea, Macedonia, Spain, Turkey, and the USA). DNA source for *JAK2V617F* allele burden quantification was derived from various cells (e.g., bone marrow, granulocytes, and leukocytes), assessed using different polymerase chain reaction (PCR) and sequencing techniques. Six studies collected samples exclusively at diagnosis, eight studies had a mix of samples at diagnosis and during follow-ups, one study had only follow-up samples, and six studies did not report the collection time point.

Thirteen studies employed correlation tests for *JAK2V617F* with clinical correlates, while ten studies categorized patients into low and high allele burden groups. Notably, despite the initial screening of clinical trials, relevant evidence for our objectives came from cross-sectional and cohort studies, as clinical trials did not investigate the association between clinical characteristics and allele burden. A summary of the risk of bias assessment using the JBI checklist is provided in Supplemental Information 2.

Meta-analyses of correlation

We examined the correlation of *JAK2V617F* allele burden with blood cell counts and spleen size. WBC and RBC were significantly and positively correlated with *JAK2V617F* allele burden, whereas PLT was not significantly correlated with *JAK2V617F* allele burden. In addition, spleen size was significantly and positively correlated with *JAK2V617F* allele burden.

Table 1 Study details on JAK2V617F allele burden measurement and data presentation with clinical correlates

Author [ref]	Year	Country	N	DNA source	JAK2V617F quantification	Samples at dx	Data presentation	Clinical correlates	Statistical methods
Alvarez-Larran	2014	Spain	163	Granulocytes	AS-qPCR	Some	Dichotomous (50%)	Thrombosis; MF transformation	KM analysis; multivariate poisson regression
Bai	2015	China	272	PB granulocytes	AS-qPCR	All	Dichotomous (50%)	PLT; WBC; Thrombosis; MF transformation	Independent t-test; MWU test; KM analysis; univariate/multivariate Cox regression
Barbui	2011	Italy	71	PB	Not stated	Some	Dichotomous (50%)	High-sensitivity C-reactive protein; pentraxin-3	Multivariate regressions; univariate/multivariate logistic regressions
Bellanne-Chantelot	2006	Belgium, France	81	PB mononuclear cells; BM cells; EEC	PCR	No	Dichotomous (50%)	Disease duration; Hb; Hct; PLT; WBC; hematological complications; splenomegaly; thrombosis; OS; EEC status	Chi-square test; Fisher exact test; KW test; KM analysis
Carobbio	2009	Italy	415	Not stated	qRT-PCR	Some	Trichotomous (1–25%; 26–50%; >50%)	Thrombosis	Chi-square test; Fisher exact test; WRS test; KM analysis; test for trend of the survivor function; multivariate Cox regression
Cokic	2015	Serbia	92	PB granulocytes	PCR	All	Dichotomous (50%)	Hb; MCV; RBC; PLT; WBC; CD34+ cell count	Independent t-test
Coucelo	2014	Portugal	31	PB	AS-qPCR; qRT-PCR	Not stated	Continuous	PMN aggregates; CD11b expressions; CD63 expression; monocyte TF expression	Spearman correlation; t-test
Edahiro	2014	Japan	66	PB mononuclear cells	ABC-PCR; AS-qPCR	All	Continuous	Hb; PLT; WBC	Pearson correlation
Ferdowsi	2015	Iran	20	PB leukocytes	qRT-PCR	All	Continuous	Hb; PLT; WBC	Spearman correlation
Ferdowsi	2016	Iran	51	PB leukocytes	qRT-PCR	Some	Continuous	Hb; PLT; WBC	Spearman correlation
Gangat	2008a	USA	418	BM	qRT-PCR	All	Dichotomous (pruritus yes/no)	Pruritus	Raw data
Gangat	2008b	USA	137	BM	AS-qPCR	All	Trichotomous (1–25%; 26–50%; 51–75%)	Cytogenetics	Undetermined
Gangemi	2012	Italy	20	PB	AS-qPCR	Not stated	Continuous	WBC; pruritus	Spearman correlation

Table 1 (continued)

Author [ref]	Year	Country	N	DNA source	JAK2V617F quantification	Samples at dx	Data presentation	Clinical correlates	Statistical methods
Guglielmelli	2021	Italy	865	Not stated	Not stated	All	Dichotomous (50%)	Age; gender; history of thrombosis; history of hemorrhage; Hb; Hct; PLT; WBC; LDH; pruritus; splenomegaly; thrombosis; MF transformation; leukemic transformation	Chi-square test; MWU test; KM analysis; Cox proportional hazard regression (univariate and multivariate)
Ha	2012	South Korea	22	BM	Pyrosequencing	All	Quaternary (1–25%; 25–50%, 50–75%, 75–100%)	Age; Hb; Hct; PLT; WBC; neutrophil count; organomegaly; thrombotic event; fibrosis	Independent t-test; one-way ANOVA
Hu	2017	China	20	BM; PB	AS-qPCR	All	Continuous	PLT	Pearson correlation
Koren-Michowitz	2012	Israel	101	PB mononuclear cells	Quantitative chip-based MALDI-TOF MS	Not stated	Continuous; dichotomous (clinical correlates)	Gender; ethnicity; disease duration; spleen size; symptoms; pruritus; erythromelalgia; vascular complications; disease transformations; cytoreductive therapy	Spearman correlation; WRS test
Larsen	2007	Denmark	95	PB leukocytes	qRT-PCR	Some	Continuous; dichotomous (50%)	Age; gender; disease duration; Hb; Hct; PLT; WBC; CD34; LDH; thrombosis; cytoreductive therapy; PRV-1	Spearman correlation; WRS test
Lee	2021	South Korea	61	PB	Direct sequencing	Not stated	Dichotomous (58%)	Age at diagnosis; gender; Hb; Hct; PLT; WBC; LDH; thrombosis at diagnosis and follow-up; MF progression; OS	Chi-square test; MWU test; KM analysis; univariate/multivariate logistic regressions
Lekovic	2017	Serbia	30	PB granulocytes	AS-qPCR; fragment analysis	Some	Dichotomous (50%)	Plasma vascular endothelial growth factor; plasma basic fibroblast growth factor; plasma interleukin-8	Independent t-test
Malak	2012	Belgium, France	97	PB mononuclear cells	Direct sequencing; PCR	Some	Dichotomous (50%)	MF transformation; leukemic transformation	Chi-square test; Fisher exact test
Maslah	2022	France	129	PB whole blood	AS-qPCR	Not stated	Continuous	RCM	Correlation test
Moliterno	2008	USA	138	PB neutrophils, CD4+ cells	AS-qPCR	Some	Continuous; dichotomous (clonal dominance)	Disease duration; PLT; WBC; reticulocyte; spleen size	Correlation test; Independent t-test
Okabe	2016	Japan	74	BM or PB mononuclear cells	MB-PCR; direct sequencing	Not stated	Continuous; dichotomous (70%)	Age; gender; history of thrombosis; history of hemorrhage; vascular risk factors; Hb; Hct; RBC; PLT; WBC; leukocyte ALP; Vitamin 12; chromosomal abnormality; MF transformation; leukemic transformation; therapy	Chi-square test, Fisher's exact test, and independent t-test; Pearson correlation

Table 1 (continued)

Author [ref]	Year	Country	N	DNA source	JAK2V617F quantification	Samples at dx	Data presentation	Clinical correlates	Statistical methods
Passamonti	2010	Italy	338	Granulocytes	qRT-PCR	Some	Continuous; dichotomous (50%)	Disease duration; Hb; PLT; WBC; pruritus; spleen size thrombosis; hemorrhage; MF transformation; leukemic transformation; MF-free survival; (age-adjusted) BM cellularity	Spearman correlation; KM test; Multivariate Cox regression
Payzin	2014	Turkey	81	Not stated	AS-qPCR	Some	Continuous; dichotomous (50%)	Age; Hb; PLT; WBC; LDH; spleen size	Undetermined
Pieri	2009	Italy	78	PB neutrophils, basophils	ARMS-PCR; QRT-PCR	Not stated	Continuous; dichotomous (50%)	Basophil count; CD63 + basophil count; pruritus; history of thrombosis	Spearman correlation; MWU test
Popova-Labachevska	2019	Macedonia	17	Not stated	AS-qPCR	Not stated	Trichotomous (< 10%; 10–50%; > 50%)	Age; Hb; Hct; RBC; PLT; WBC	KW test
Ruella	2013	Italy	78	PB leukocytes	AS-qPCR	Some	Dichotomous (50%)	Telomere length	Multivariate ANCOVA
Sacco	2020	Italy	48	PB mononuclear cells	qRT-PCR	Not stated	Continuous	Age; gender; RBC; PLT; VWF: Act; VWF: Ag; HU treatment; splenomegaly	Spearman correlation
Sazawal	2019	India	90	PB granulocytes	qRT-PCR	Not stated	Dichotomous (clinical correlates)	Age; gender; Hb; Hct; PLT; WBC; splenomegaly; thrombosis	Undetermined
Silver	2011	USA	105	PB leukocytes	ARMS-PCR; pyrosequencing	Some	Dichotomous (MF grade; thrombosis type); quarternary (spleen size); quinary (0–20%; 21–40%; 41–60%; 61–80%; 81–100%)	Disease duration; WBC; spleen size; thrombosis type; MF grade	Independent t-test; ANOVA
Stein	2011	USA	161	PB	AS-qPCR	Some	Dichotomous (50%); OR	Gender; thrombosis	Multivariate logistic regression
Stein	2013	USA	204	PB	AS-qPCR	Not stated	Dichotomous (age)	Age	WRS test
Tefferi	2007	USA	186	BM	qRT-PCR	Some	Continuous	Age; gender; Hb; PLT; WBC; pruritus; microvascular symptoms; palpable splenomegaly; major thrombosis; thrombosis type	Multivariate linear regression

Table 1 (continued)

Author [ref]	Year	Country	N	DNA source	JAK2V617F quantification	Samples at dx	Data presentation	Clinical correlates	Statistical methods
Vannucchi	2007a	Italy	173	PB granulocytes	ARMS-PCR; QRT-PCR	All	Continuous; quaternary (1–25%; 25–50%, 50–75%, 75–100%); RR	Gender; Hct; MCV; PLT; WBC; neutrophil count; LDH; leukocyte ALP; erythropoietin; ferritin; systemic symptoms; pruritus; splenomegaly; spleen size; thrombosis; therapy; cytoreduction-free survival; PRV-1	Chi-square test; Fisher exact test; MWU test; KW test; Spearman correlation; KM test; logistic regression
Vannucchi	2007b	Italy	323	PB granulocytes	AS-qPCR	Some	Continuous; dichotomous (50%)	Age; gender; disease duration; Hct; PLT; WBC; systemic symptoms; pruritus; splenomegaly; CV event; therapy	Chi-square test, Fisher's exact test, and independent t-test; Cox regressions; logistic regressions
Zhao	2016	China	54	BM mononuclear cells	AS-qPCR	All	Continuous; dichotomous (clinical correlates)	Age; gender; Hb; PLT; WBC; splenomegaly; thrombosis	Chi-square test; Pearson correlation; Independent t-test; MWU test; KM test; Cox regression
Zhou	2013	China	57	BM; PB cells	AS-qPCR	Not stated	Continuous	RBC; PLT; WBC; erythropoiesis; granulopoiesis	Spearman correlation

ABC-PCR: alternately binding probe competitive polymerase chain reaction; ANCOVA: analysis of covariance; ANOVA: analysis of variance; ALP: alkaline phosphatase; ARMS-PCR: amplification-refractory mutation sequencing polymerase chain reaction; AS-qPCR: allele specific real-time polymerase chain reaction; BM: bone marrow; dx: diagnosis; CD: cluster of differentiation; CV: cardiovascular; EEC: endogenous erythroid colony; Hb: hemoglobin; Hct: hematocrit; KM: Kaplan-Meier; KW: Kruskal-Wallis; LDH: lactate dehydrogenase; MALDI-TOF MS: matrix-assisted laser desorption-time-of-flight mass spectrometry; MB-PCR: mutation biased polymerase chain reaction; MCV: mean corpuscular volume; MF: myelofibrosis/myelofibrotic; MWU: Mann-Whitney U; N: number of polycythemia vera patients included in the study; OR: odds ratio; OS: overall survival; PB: peripheral blood; PLT: platelet count; PMN: polymorphonuclear; PRV-1: polycythemia rubra vera 1; qRT-PCR: quantitative real-time polymerase chain reaction; RCM: red cell mass; RR: relative risk; TF: tissue factor; USA: United States of America; VWF: Act: von Willebrand factor activity; VWF: Ag: von Willebrand factor antigen; WBC: white blood cell count; WRS: Wilcoxon rank-sum

Ten cohorts (703 patients) reported a significant and positive correlation between *JAK2V617F* allele burden and WBC (Fig. 2A: $r=0.329$; 95%CI=[0.145,0.491]; $p=0.001$; TauSq=0.080). Sub-group analysis for the three cohorts (293 patients) with samples collected at diagnosis, demonstrated a significant and positive correlation ($r=0.514$; 95% CI=[0.223,0.721]; $p=0.001$). For the seven cohorts (410 patients) with samples collected at mixed or unstated time points, a near-significant and positive correlation was observed ($r=0.226$; 95% CI=[-0.009,0.438]; $p=0.060$). Pooled within-group TauSq was 0.077. Total between-group heterogeneity was as follows: $Q=2.526$; $df=1$; $p=0.112$.

Ten cohorts (723 patients) demonstrated a non-significant correlation between *JAK2V617F* allele burden and PLT (Fig. 2B: $r=0.019$; 95%CI=[-0.185,0.221]; $p=0.860$; TauSq=0.080). Sub-group analysis for two cohorts (389 patients) with samples collected at diagnosis showed a non-significant correlation ($r=0.023$; 95% CI=[-0.390,

0.429]; $p=0.916$). For eight cohorts (334 patients) with samples collected at mixed or unstated time points, a non-significant correlation was observed ($r=0.017$; 95% CI=[-0.213, 0.246]; $p=0.885$). Pooled within-group TauSq was 0.088. Total between-group heterogeneity was as follows: $Q=0.001$; $df=1$; $p=0.980$.

Three studies (179 patients) reported a significant and positive correlation between *JAK2V617F* allele burden and RBC (Fig. 2C: $r=0.219$; 95% CI=[0.073,0.357]; $p=0.004$; TauSq=0.000). Two studies (240 patients) reported a significant and positive correlation between *JAK2V617F* allele burden and spleen size (Fig. 2D: $r=0.329$; 95% CI=[0.153,0.484]; $p<0.001$; TauSq=0.009). Neither Hb levels nor Hct (Supplemental Information 3, SI3) correlated significantly with allele burden, which respectively included four and two studies.

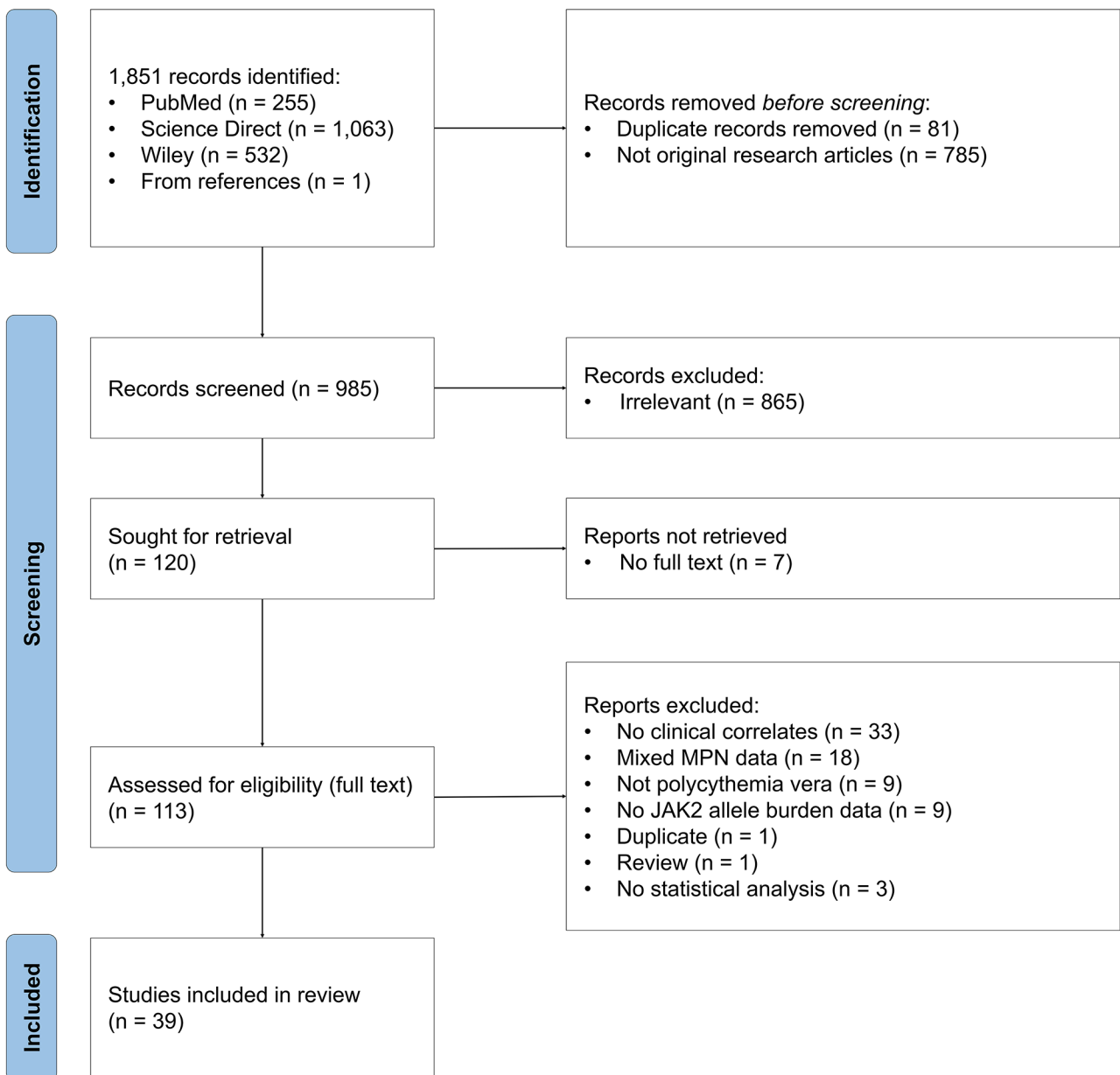


Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram describing the identification, screening, and inclusion process

Meta-analyses of standardized mean difference

We explored the SMD in clinical correlates between patients with high or low *JAK2V617F* allele burden. WBC, Hct, and lactate dehydrogenase were significantly higher in patients with higher *JAK2V617F* allele burden, whereas PLT was significantly lower in patients with higher *JAK2V617F* allele burden. In addition, Hb and RBC were not significantly different between allele burden groups.

Nine cohorts (1,545 patients) demonstrated a significant SMD, indicating higher WBC in patients

with a higher *JAK2V617F* allele burden (Fig. 3A: SMD=0.549; SE=0.212; 95%CI=[0.134,0.964]; $p=0.010$; TauSq=0.333). Similarly, nine cohorts (1,545 patients) reported a significant SMD in PLT, revealing that patients with a higher *JAK2V617F* allele burden had lower PLT (Fig. 3B: SMD=-0.947.; SE=0.307; 95%CI=[-1.548,-0.346]; $p=0.002$; TauSq=0.762). Seven cohorts (1,421 patients) indicated a significant SMD, with higher Hct in patients with a higher *JAK2V617F* allele burden (Fig. 3C: SMD=0.365; SE=0.134; 95% CI=[-0.102,0.627]; $p=0.006$; TauSq=0.080). Four studies (804

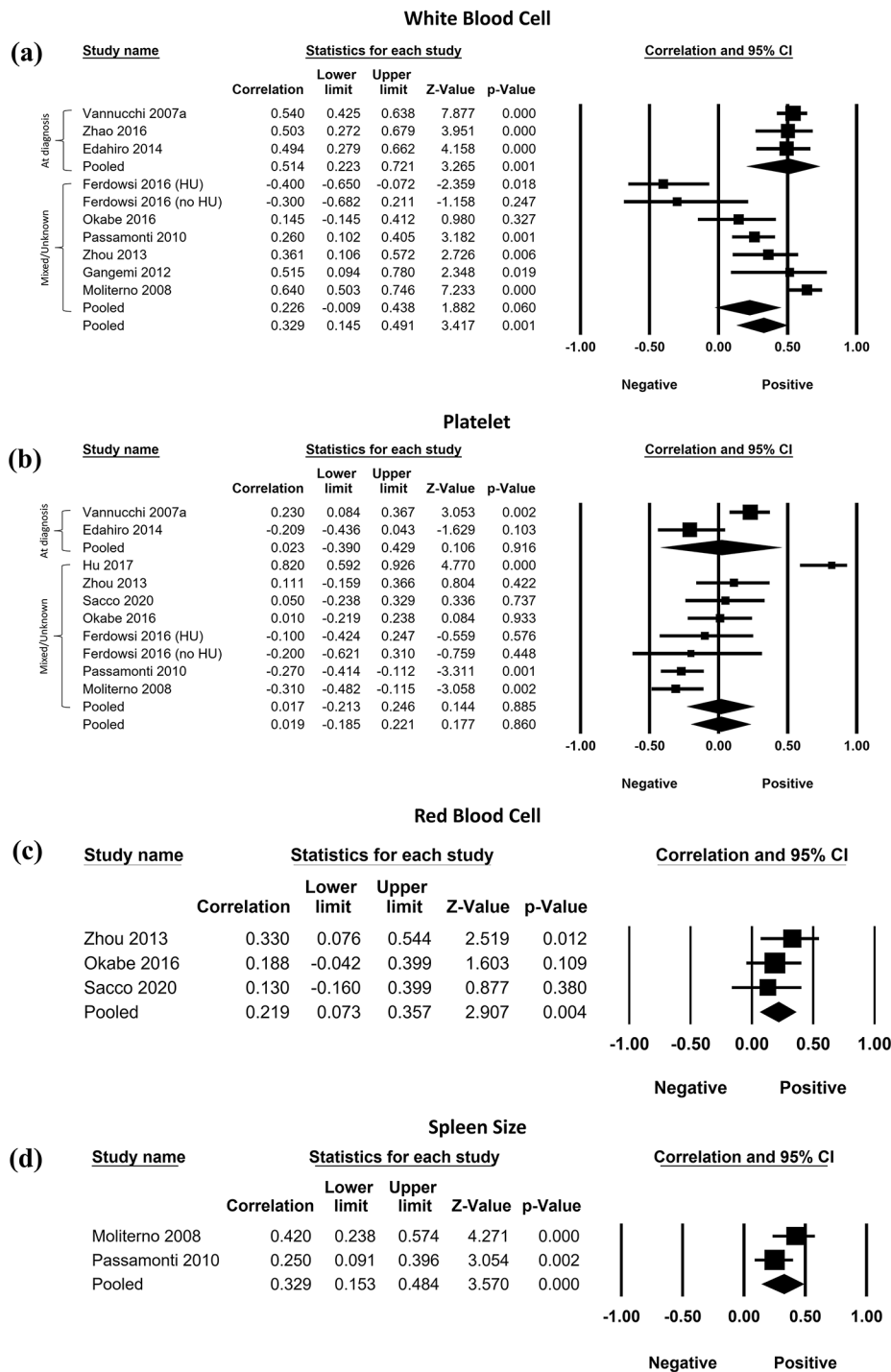


Fig. 2 Forest plots of meta-analyses of correlation coefficient of JAK2V617F allele burden vs. (a) white blood cell count, (b) platelet, (c) red blood cell, and (d) spleen size. Sub-group analysis was con-

ducted for (a) and (b) to examine the difference between samples collected at diagnosis and those collected at mixed or unstated timepoints

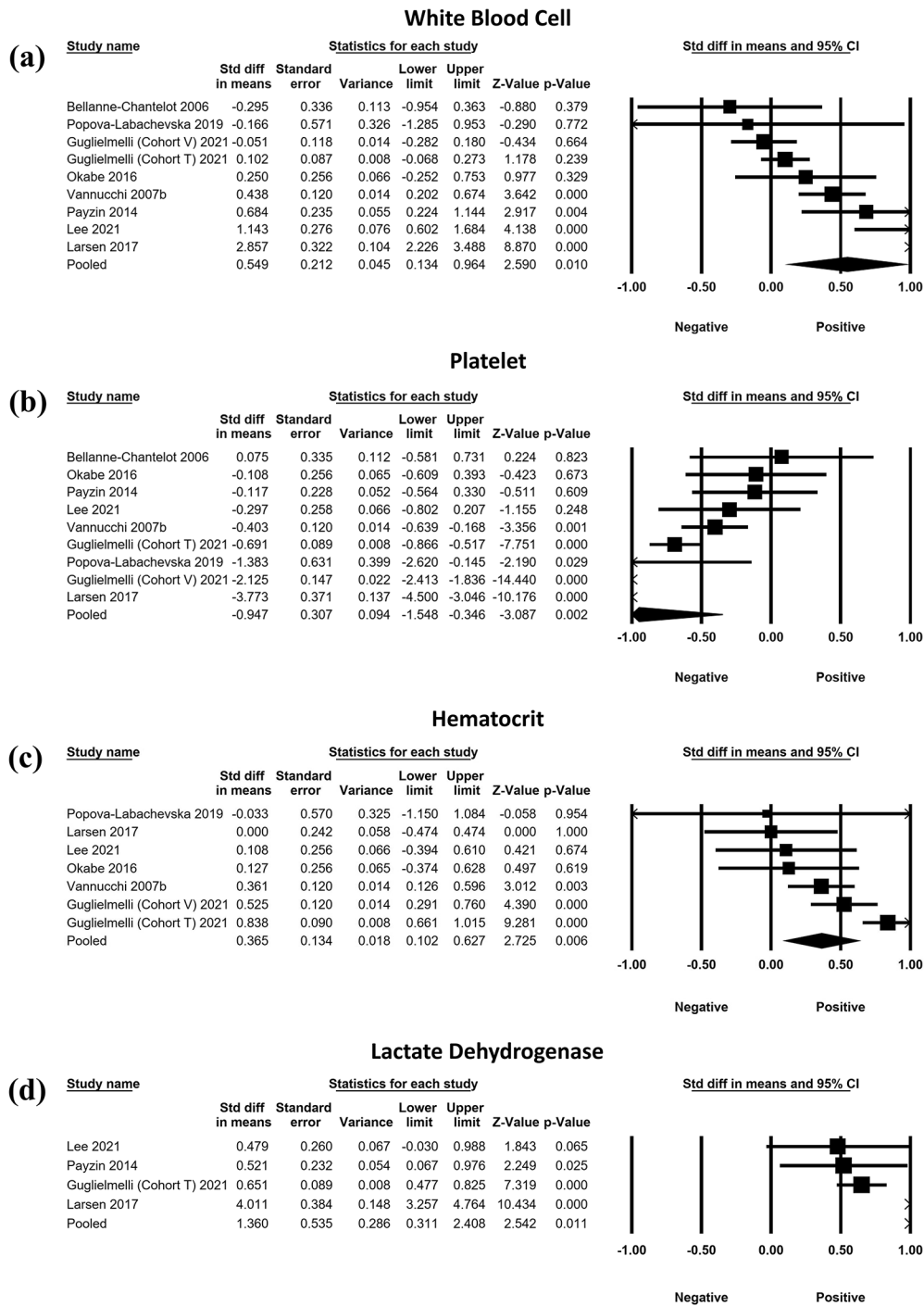


Fig. 3 Forest plots of meta-analyses of standardized mean difference of (a) white blood cell count, (b) platelet, (c) hematocrit, and (d) lactate dehydrogenase, by allele burden group (high allele burden vs. low allele burden group)

patients) indicated a significant SMD, with higher lactate dehydrogenase in patients with a higher *JAK2V617F* allele burden (Fig. 3D: SMD=0.1360; SE=0.535; 95% CI=[0.311,2.408]; $p=0.011$; TauSq=1.078). The SMDs of Hb and RBC (SI3) between high and low allele burden groups were not significantly different, involving five and two studies, respectively.

Meta-analyses of odds ratio

We investigated the odds ratio (OR) of developing symptoms or complications with higher *JAK2V617F* allele burden. We found that patients who had higher *JAK2V617F* allele burden also had a significantly greater OR for developing pruritus, splenomegaly, thrombosis and transformation to MF or AML.

Four cohorts (1,233 patients) reported a significant OR for pruritus, indicating that patients with higher *JAK2V617F* allele burden had a greater OR for developing pruritus (Fig. 4A: OR=2.200; 95% CI=[1.512,3.199]; $p<0.001$; TauSq=0.070). Six cohorts (1,388 patients) reported a significant OR for splenomegaly, indicating that patients with higher *JAK2V617F* allele burden had a greater OR for developing splenomegaly (Fig. 4B: OR=2.133; 95%

CI[1.415,3.214]; $p<0.001$; TauSq=0.123). Six cohorts (1,616 patients) reported a significant OR for thrombosis, indicating that patients with higher *JAK2V617F* allele burden had a greater OR for developing thrombosis (Fig. 4C: OR=1.882; 95% CI=[1.179,3.003]; $p=0.008$; TauSq=0.154). *JAK2V617F* allele burden did not seem to significantly affect the odds of thrombosis history in our meta-analyses (Fig. 4D). Seven cohorts (1522 patients) reported a significant OR for MF transformation, revealing that patients with higher *JAK2V617F* allele burden had a greater OR for MF transformation (Fig. 4E: OR=8.214; 95% CI=[5.157,13.083]; $p<0.001$; TauSq=0.000). Five cohorts (1,318 patients) reported a significant OR for AML progression, indicating that patients with higher *JAK2V617F* allele burden had a greater OR for AML transformation (Fig. 4F: 2.122; 95% CI=[1.074,4.192]; $p=0.030$; TauSq=0.000).

Qualitative analysis of patients categorized by clinical characteristics

Several studies examined the *JAK2V617F* allele burden in patients categorized by hemogram thresholds or the presence of a symptom/complication. Consistent with both our meta-analysis on WBC, three studies identified higher

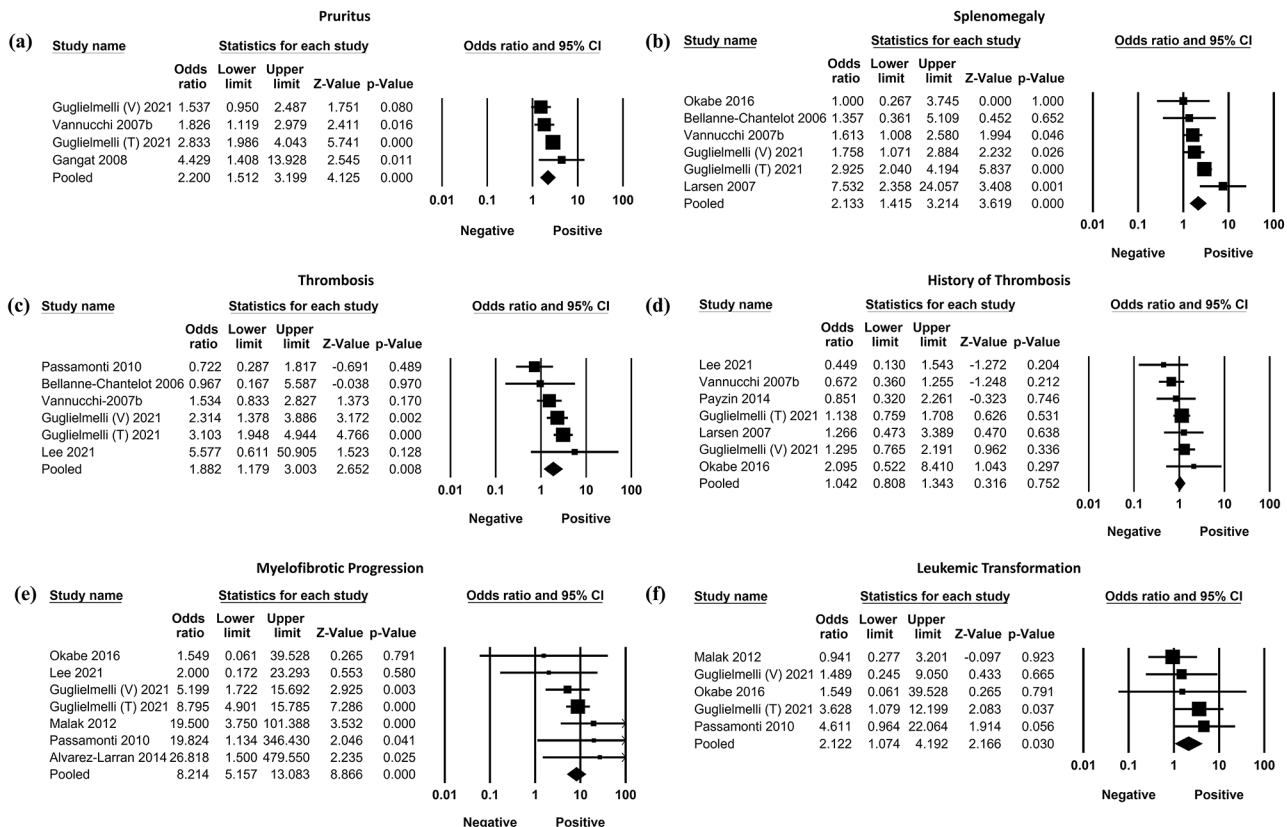


Fig. 4 Forest plots of meta-analyses of odds ratio of (a) pruritus, (b) splenomegaly, (c) thrombosis, (d) history of thrombosis, (e) myelofibrotic progression, (f) transformation to acute myeloid leukemia, by allele burden group (high allele burden vs. low allele burden group)

JAK2V617F allele burdens in PV patients with elevated WBC [40, 41, 47]. As stated above, two studies echoed our finding of a negative association between PLT and *JAK2V617F* allele burden [40, 47].

In terms of splenomegaly, three studies [26, 40, 41] supported our correlation meta-analysis in which spleen size was positively correlated with allele burden. One study [45] found that the risk ratio for splenomegaly and spleen size over 15 cm was higher when comparing patients with low allele burden to patients with high allele burden (0–25% vs. 51–75% and 75–100%); two studies [33, 47] found similar trends between spleen size and allele burden.

For thrombosis, Vannucchi et al. [45] found a significantly higher risk ratio for total thrombosis at follow-up in patients with an allele burden of 75–100% compared to patients with an allele burden of 0–25%. Alvarez-Larran et al. [9] found that patients with *JAK2V617F* allele burden greater or equal to 50% had a higher incidence of thrombosis. Sazawal et al. [40] found that those patients who had experienced a thrombosis event also had a higher allele burden; one study [24] found a similar trend, whereas another study [47] did not.

Finally, Vannucchi et al. [45] found a significantly higher risk ratio for pruritus in patients with 50–75% and 75–100% allele burden. Koren-Michowitz et al. [26] reported a trend for higher allele burden with presence of pruritus; however, this was not significant.

Discussion

Interpretation

This review integrates data from 39 publications, encompassing approximately 5,462 patients. To the best of our knowledge, our study represents the first concerted effort to comprehensively evaluate and synthesize the existing literature on the association between *JAK2V617F* allele burden and clinical correlates in PV. Despite over 15 years since the initial discovery of this association, the difficulty of obtaining high-quality data may have impeded previous publications and systematic reviews on this subject. Our combined qualitative analysis and meta-analysis reveal a robust positive association between *JAK2V617F* allele burden and WBC, along with an increased risk of MF transformation. Additionally, positive associations were observed with Hct, RBC, pruritus, splenomegaly, thrombosis, and an increased risk of transformation to AML, while a negative association was noted with PLT.

Our study contributes insights into the association between *JAK2V617F* allele burden and various hematological parameters. The results unequivocally confirm a positive

association between *JAK2V617F* allele burden and WBC in PV patients. However, relationships with RBC count, Hct, and Hb levels are less conclusively established. Our meta-analysis of correlation suggests a positive association with RBC, while our meta-analysis of SMD indicates a positive association with Hct, implying some evidence of a positive association between erythrocyte-related parameters and *JAK2V617F* allele burden. Moreover, the intriguing observation of a negative association between PLT and *JAK2V617F* allele burden suggests a potential shift from thrombopoiesis to myelopoiesis when *JAK2V617F* allele burden is elevated, warranting exploration into the biological processes influencing this phenomenon.

Our study explored the association between *JAK2V617F* allele burden and thrombosis, wherein a positive association was observed. Despite the few studies included in meta-analysis, it is crucial to highlight that several independent studies, although could not be synthesized in our meta-analysis, have also presented compelling evidence for a robust association between *JAK2V617F* allele burden and thrombosis [9, 40, 45]. Vannucchi et al. [45] categorized 173 patients into four distinct groups according to their *JAK2V617F* allele burden. They observed that patients with an allele burden of 75% or higher exhibited a significantly elevated risk of thrombosis during the follow-up period. However, due to the scarcity of studies segmenting patients into four groups based on *JAK2V617F* allele burden, a meta-analysis was not feasible. In a similar vein, Alvarez-Larran et al. [9] classified 163 patients into two groups based on their *JAK2V617F* allele burden. Their findings revealed that patients with an allele burden exceeding 50%, or those with fluctuating *JAK2V617F* allele burden, demonstrated a significantly increased incidence of thrombosis. Nevertheless, the absence of comparable studies assessing incidence rates precluded the possibility of conducting a meta-analysis. Additionally, Sazawal et al. [40] stratified 45 patients based on the occurrence of thrombosis events. They found that patients experiencing a thrombosis event had a significantly higher *JAK2V617F* allele burden compared to those without such events. However, the limited number of studies that classified patients based on the occurrence of thrombosis events rendered a meta-analysis unattainable.

Our study also delves into the association between *JAK2V617F* allele burden and symptomatic manifestations as well as disease progression. Concerning spleen size, despite a limited number of studies available for meta-analysis, additional studies [26, 40, 41] reported consistent results, affirming the positive correlation between *JAK2V617F* allele burden and splenomegaly. Similarly, pruritus gains additional validation from another study [26], which reinforces the association between pruritus and *JAK2V617F* allele burden. Furthermore, our study underscores a robust

body of evidence linking a high *JAK2V617F* allele burden with an increased risk of MF transformation. This observation posits that elevated *JAK2V617F* allele burden serves as a predictor for MF transformation. Lastly, our study also observed some evidence of positive association between a high *JAK2V617F* allele burden with an increased risk of AML transformation.

In addition to our data synthesis efforts, our investigation reviewed studies that presented valuable insights into the association between *JAK2V617F* allele burden and specific clinical parameters. Notably, a substantial number of studies focused on the relationship between *JAK2V617F* allele burden and splenomegaly, thrombosis, and pruritus, which could have provided further data of 597, 502, and 274 patients, respectively. The majority of these studies consistently reported a statistically significant positive association between *JAK2V617F* allele burden and the aforementioned clinical factors.

Limitations of evidence and review process

One of the primary constraints in our work stems from the heterogeneity that impeded data synthesis. Despite the identification of 39 studies examining the relationship between the *JAK2V617F* allele burden and clinical correlates, the varied methods of data presentation and statistical analyses prevented the execution of high-quality meta-analyses. For instance, we encountered 16 studies reporting data on allele burden and WBC, of which only 9 could be incorporated into a correlation meta-analysis. Among the remaining 7 papers, data were presented in diverse formats, such as the stratification of data into two to five allele burden groups, and values reported as mean only, mean and range, median and range, median and 95%CI, and mean \pm standard deviation. Unfortunately, the inadequate homogeneity across the available studies hindered the synthesis of data, thereby impeding the extraction of conclusive insights.

The reliability of hemogram data may be susceptible to bias owing to the influence of clinical treatments. Among the parameters relevant to erythrocyte count, the most significant variability may arise from phlebotomy. Furthermore, careful consideration is advised when interpreting blood samples obtained during routine check-ups post-diagnosis, as they may be susceptible to underestimation attributed to ongoing treatments such as phlebotomy or the administration of cytoreductive agents. For example, treatment with interferon alpha has been demonstrated to effectively diminish the *JAK2V617F* allele burden, as evidenced by studies from Ianotto et al. [123] and Kiladjian et al. [124]. This reduction in allele burden may subsequently impact the risks associated with thrombosis, myelofibrotic transformation, and leukemic transformation. Consequently, these

treatments influence not just the *JAK2V617F* allele burden but also bear significant implications for the long-term outcomes of patients. This complexity adds a layer of challenge to the interpretation of data in this context.

Several assumptions were employed to address heterogeneity during data synthesis. Firstly, heterogeneity arose from the diverse statistical methods used for the meta-analysis of correlation. For example, correlation tests were assumed the same when eleven studies used Spearman's correlation, four studies used Pearson's correlation, and two studies did not report the type of correlation test. Secondly, another source of heterogeneity in the meta-analysis of SMD and OR stemmed from the varying cut-off values for *JAK2V617F* allele burden. While the majority of studies divided the patients using a 50% *JAK2V617F* allele burden as a cut-off, one study used 58% [28] and another used 70% [33]. Although a 50% cut-off represents the separation of heterozygosity and homozygosity, using a higher cut-off could better reflect the true impact of *JAK2V617F* allele burden on clinical correlates, such as a more accurate representation of the risk of thrombosis. Thirdly, the inclusion years in our systematic review spanned from 2007 to 2022, during which various diagnostic criteria for PV were utilized, including Polycythemia Vera Study Group (PVSG), World Health Organization (WHO) 2008, and WHO 2016 classification. Consequently, the criteria were not consistent across all studies, and it was assumed that patients diagnosed under different criteria were similar. Lastly, there were differences among studies in the biological samples collected and the methods used to quantify *JAK2V617F* allele burden.

Implications

Based on our findings, we propose several suggestions for future research aiming to investigate the association between *JAK2V617F* allele burden and clinical correlates. Firstly, detailing the specific time point of sample collection (e.g., at diagnosis, before treatment, or after treatment) is crucial information to include, given the potential impact of certain treatments on *JAK2V617F* allele burden and clinical correlates. Particularly for measurements related to erythrocytes, it is essential to explicitly include Hb, Hct, and RBC without recent phlebotomy, preferably within a three-month timeframe. Attention to the timing of blood sample collection concerning treatment regimens is critical for a more accurate assessment of the relationship between *JAK2V617F* allele burden and hematological parameters across the entire hemogram. Secondly, considering the heterogeneity in study design, data presentation, and statistical methods, the limited amount of data available for synthesis underscores the need for improved feasibility in future meta-analyses. We recommend that researchers consider

providing additional data or statistical analyses as supplemental information. Alternatively, utilizing data repositories for sharing relevant datasets could enhance collaboration and facilitate more comprehensive meta-analyses.

This review highlights the varying degrees of association between *JAK2V617F* allele burden and clinical correlates. While some might intuitively infer that reducing *JAK2V617F* allele burden could benefit the status and prognosis of patients, others may argue that a mere observation of association does not necessarily imply a call for action. Nevertheless, there are preliminary data suggesting the potential benefits of reducing *JAK2V617F* allele burden. For instance, a retrospective study involving 381 MPNs patients treated with interferon revealed that approximately 50% of patients who achieved complete hematological response and maintained a *JAK2V617F* allele burden below 10% did not have a relapse for at least ten years after discontinuing interferon treatment [125]. A Phase II clinical trial, MAJIC-PV, comparing ruxolitinib with the best available therapy in patients with PV who are resistant or intolerant to hydroxyurea, demonstrated a higher frequency of molecular responses in those treated with ruxolitinib [126]. Additionally, indirect evidence from molecular analyses and clinical correlations indicates that patients achieving a partial molecular response exhibit improved outcomes in terms of progression-free survival, event-free survival, and overall survival [126]. Another indirect piece of evidence comes from the Continuation-PV study, where patients receiving ropeginterferon alfa-2b demonstrated a general reduction in *JAK2V617F* allele burden and experienced fewer thromboembolic events, less disease progression, and fewer deaths [127]. These findings suggest that novel therapeutic interventions aimed at lowering allele burden could improve not only hemogram but could also manage symptoms, reduce thrombosis risks, and reduce risks of disease progression [128]. Of which, reducing the risks of thrombosis and disease progression are especially important from the perspective of patients [129]. However, a real-world nationwide study in Taiwan showed that around 48.8% low-risk and 26.1% high-risk PV patients were not undergoing active treatment [130]. Additionally, another study in the United States based on a veteran database reported that 53% of patients were not receiving active treatment [131]. As there are some evidence showing that *JAK2V617F* allele burden may progressively increase with age [24, 27, 40, 43, 44], patients without active treatment or monitoring *JAK2V617F* allele burden may be prone to worse outcomes. The rate of clonal expansion exhibits considerable variability among individuals. While some of this variation may be intrinsic, it may also be linked to the type of treatment received by the patient. This relationship underscores the intricate interplay between therapeutic interventions and cellular responses.

However, a significant limitation in the current research landscape is the predominance of studies focusing solely on single time point measurements. This methodological constraint restricts the depth of understanding regarding the dynamic nature of clonal expansion over time and its interactions with various treatments. Further research on the clinical value of the long-term monitoring of *JAK2V617F* allele burden could prove valuable in inferring prognosis, guiding monitoring strategies, and designing treatment plans.

This systematic review and its protocol were registered in the international prospective register of systematic reviews (PROSPERO) under the registration number: CRD42024219346.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests Dr. Justin L. Chen was a contract researcher for Panco Healthcare Co., Ltd, a Pharmaessentia Company. Mr. Alex Jia-Hong Lin and Dr. Lennex Hsueh-Lin Yu are full-time employees for Panco Healthcare Co., Ltd, a Pharmaessentia Company. Dr. Hsin-An Hou and Dr. Chih-Cheng Chen declare honorarium, travel, and research support from PharmaEssentia Corporation.

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References

- Baxter EJ, Scott LM, Campbell PJ et al (2005) Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders [published correction appears in *Lancet*. 2005 Jul 9–15;366(9480):122]. *Lancet* 365(9464):1054–1061. [https://doi.org/10.1016/S0140-6736\(05\)71142-9](https://doi.org/10.1016/S0140-6736(05)71142-9)
- Levine RL, Wadleigh M, Cools J et al (2005) Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. *Cancer Cell* 7(4):387–397. <https://doi.org/10.1016/j.ccr.2005.03.023>
- Garçon L, Rivat C, James C et al (2006) Constitutive activation of STAT5 and Bel-xL overexpression can induce endogenous erythroid colony formation in human primary cells. *Blood* 108(5):1551–1554. <https://doi.org/10.1182/blood-2005-10-009514>
- Kralovics R, Teo SS, Li S et al (2006) Acquisition of the V617F mutation of JAK2 is a late genetic event in a subset of patients with myeloproliferative disorders. *Blood* 108(4):1377–1380. <https://doi.org/10.1182/blood-2005-11-009605>
- Rane SG, Reddy EP (2002) JAKs, STATs and Src kinases in hematopoiesis. *Oncogene* 21(21):3334–3358. <https://doi.org/10.1038/sj.onc.1205398>
- Akada H, Yan D, Zou H et al (2010) Conditional expression of heterozygous or homozygous Jak2V617F from its endogenous promoter induces a polycythemia vera-like disease. *Blood* 115(17):3589–3597. <https://doi.org/10.1182/blood-2009-04-215848>
- Nangalia J, Green TR (2014) The evolving genomic landscape of myeloproliferative neoplasms. *Hematol Am Soc Hematol Educ Program* 2014(1):287–296. <https://doi.org/10.1182/asheducation-2014.1.287> Epub 2014 Nov 18. PMID: 25696868
- Scott LM, Tong W, Levine RL et al (2007) JAK2 exon 12 mutations in polycythemia vera and idiopathic erythrocytosis. *N Engl J Med* 356(5):459–468. <https://doi.org/10.1056/NEJMoa065202>
- Alvarez-Larrán A, Bellosillo B, Pereira A et al (2014) JAK2V617F monitoring in polycythemia vera and essential thrombocythemia: clinical usefulness for predicting myelofibrotic transformation and thrombotic events. *Am J Hematol* 89(5):517–523. <https://doi.org/10.1002/ajh.23676>
- Page MJ, McKenzie JE, Bossuyt PM et al (2021) Updating guidance for reporting systematic reviews: development of the PRISMA 2020 statement. *J Clin Epidemiol* 134:103–112. <https://doi.org/10.1016/j.jclinepi.2021.02.003>
- Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P-F (2020) Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). *JBIManual for Evidence Synthesis*. JBI, <https://synthesismanual.jbi.global>
- Bai J, Ai L, Zhang L, Yang FC, Zhou Y, Xue Y (2015) Incidence and risk factors for myelofibrotic transformation among 272 Chinese patients with JAK2-mutated polycythemia vera. *Am J Hematol* 90(12):1116–1121. <https://doi.org/10.1002/ajh.24191>
- Barbui T, Carobbio A, Finazzi G et al (2011) Inflammation and thrombosis in essential thrombocythemia and polycythemia vera: different role of C-reactive protein and pentraxin 3. *Haematologica* 96(2):315–318. <https://doi.org/10.3324/haematol.2010.031070>
- Bellanné-Chantelot C, Chamarel I, Labopin M et al (2006) Genetic and clinical implications of the Val617Phe JAK2 mutation in 72 families with myeloproliferative disorders. *Blood* 108(1):346–352. <https://doi.org/10.1182/blood-2005-12-4852>
- Carobbio A, Finazzi G, Antonioli E et al (2009) JAK2V617F allele burden and thrombosis: a direct comparison in essential thrombocythemia and polycythemia vera. *Exp Hematol* 37(9):1016–1021. <https://doi.org/10.1016/j.exphem.2009.06.006>
- Čokić VP, Mitrović-Ajtić O, Beleslin-Čokić BB et al (2015) Pro-inflammatory cytokine IL-6 and JAK-STAT signaling pathway in Myeloproliferative Neoplasms. *Mediators Inflamm* 2015:453020. <https://doi.org/10.1155/2015/453020>
- Coucelo M, Caetano G, Sevivas T et al (2014) JAK2V617F allele burden is associated with thrombotic mechanisms activation in polycythemia vera and essential thrombocythemia patients. *Int J Hematol* 99(1):32–40. <https://doi.org/10.1007/s12185-013-1475-9>
- Edahiro Y, Morishita S, Takahashi K et al (2014) JAK2V617F mutation status and allele burden in classical Ph-negative myeloproliferative neoplasms in Japan. *Int J Hematol* 99(5):625–634. <https://doi.org/10.1007/s12185-014-1567-1>
- Ferdowsi S, Atarodi K, Amirzadeh N et al (2015) Expression analysis of microRNA-125 in patients with polycythemia vera and essential thrombocythemia and correlation with JAK2 allele burden and laboratory findings. *Int J Lab Hematol* 37(5):661–667. <https://doi.org/10.1111/ijlh.12381>
- Ferdowsi S, Ghaffari SH, Amirzadeh N et al (2016) JAK2V617F Allele Burden Measurement in Peripheral blood of Iranian patients with myeloproliferative neoplasms and effect of Hydroxyurea on JAK2V617F Allele Burden. *Int J Hematol Oncol Stem Cell Res* 10(2):70–78
- Gangat N, Strand JJ, Lasho TL, Li CY, Pardanani A, Tefferi A (2008) Pruritus in Polycythemia vera is associated with a lower risk of arterial thrombosis. *Am J Hematol* 83(6):451–453. <https://doi.org/10.1002/ajh.21156>
- Gangat N, Strand J, Lasho TL et al (2008) Cytogenetic studies at diagnosis in polycythemia vera: clinical and JAK2V617F allele burden correlates. *Eur J Haematol* 80(3):197–200. <https://doi.org/10.1111/j.1600-0609.2007.01003.x>
- Gangemi S, Allegra A, Pace E et al (2012) Evaluation of interleukin-23 plasma levels in patients with polycythemia vera and essential thrombocythemia. *Cell Immunol* 278(1–2):91–94. <https://doi.org/10.1016/j.cellimm.2012.07.003>
- Ha JS, Kim YK, Jung SI, Jung HR, Chung IS (2012) Correlations between Janus kinase 2 V617F allele burdens and clinicohematologic parameters in myeloproliferative neoplasms. *Ann Lab Med* 32(6):385–391. <https://doi.org/10.3343/alm.2012.32.6.385>
- Hu L, Pu L, Ding Y et al (2017) Relationship between JAK2V617F mutation, allele burden and coagulation function in Ph-negative myeloproliferative neoplasms. *Hematology* 22(6):354–360. <https://doi.org/10.1080/10245332.2016.1267830>
- Koren-Michowitz M, Landman J, Cohen Y et al (2012) JAK2V617F allele burden is associated with transformation to myelofibrosis. *Leuk Lymphoma* 53(11):2210–2213. <https://doi.org/10.3109/10428194.2012.682308>
- Larsen TS, Pallisgaard N, Møller MB, Hasselbalch HC (2007) The JAK2 V617F allele burden in essential thrombocythemia, polycythemia vera and primary myelofibrosis—impact on disease phenotype. *Eur J Haematol* 79(6):508–515. <https://doi.org/10.1111/j.1600-0609.2007.00960.x>
- Lee AJ, Kim SG, Nam JY, Yun J, Ryoo HM, Bae SH (2021) Clinical features and outcomes of JAK2 V617F-positive polycythemia vera and essential thrombocythemia according to the JAK2 V617F allele burden. *Blood Res* 56(4):259–265. <https://doi.org/10.5045/br.2021.2021089>
- Lekovic D, Gotic M, Skoda R et al (2017) Bone marrow microvessel density and plasma angiogenic factors in myeloproliferative neoplasms: clinicopathological and molecular correlations. *Ann Hematol* 96(3):393–404. <https://doi.org/10.1007/s00277-016-2890-9>
- Malak S, Labopin M, Saint-Martin C, Bellanne-Chantelot C, Najman A, French Group of Familial Myeloproliferative Disorders (2012) Long term follow up of 93 families with myeloproliferative neoplasms: life expectancy and implications of JAK2V617F

- in the occurrence of complications. *Blood Cells Mol Dis* 49(3–4):170–176. <https://doi.org/10.1016/j.bcmd.2012.06.004>
31. Maslah N, Ravdan O, Drevon L et al (2022) Revisiting diagnostic performances of serum erythropoietin level and JAK2 mutation for polycythemia: analysis of a cohort of 1090 patients with red cell mass measurement. *Br J Haematol* 196(3):676–680. <https://doi.org/10.1111/bjh.17848>
 32. Moliterno AR, Williams DM, Rogers O, Isaacs MA, Spivak JL (2008) Phenotypic variability within the JAK2 V617F-positive MPD: roles of progenitor cell and neutrophil allele burdens. *Exp Hematol* 36(11):1480–1486. <https://doi.org/10.1016/j.exphem.2008.05.006>
 33. Okabe M, Yamaguchi H, Usuki K et al (2016) Clinical features of Japanese polycythemia vera and essential thrombocythemia patients harboring CALR, JAK2V617F, JAK2Ex12del, and MPLW515L/K mutations. *Leuk Res* 40:68–76. <https://doi.org/10.1016/j.leukres.2015.11.002>
 34. Passamonti F, Rumi E, Pietra D et al (2010) A prospective study of 338 patients with polycythemia vera: the impact of JAK2 (V617F) allele burden and leukocytosis on fibrotic or leukemic disease transformation and vascular complications. *Leukemia* 24(9):1574–1579. <https://doi.org/10.1038/leu.2010.148>
 35. Payzin KB, Savasoglu K, Alacacioglu I et al (2014) JAK2 V617F mutation status of 232 patients diagnosed with chronic myeloproliferative neoplasms. *Clin Lymphoma Myeloma Leuk* 14(6):525–533. <https://doi.org/10.1016/j.clml.2014.02.013>
 36. Pieri L, Bogani C, Guglielmelli P et al (2009) The JAK2V617 mutation induces constitutive activation and agonist hypersensitivity in basophils from patients with polycythemia vera. *Haematologica* 94(11):1537–1545. <https://doi.org/10.3324/haematol.2009.007047>
 37. Popova-Labachevska M, Panovska-Stavridis I, Eftimov A et al (2019) Evaluation of the JAK2V617F mutational burden in patients with Philadelphia chromosome negative myeloproliferative neoplasms: a single-center experience. *Balkan J Med Genet* 22(2):31–36 Published 2019 Dec 21. <https://doi.org/10.2478/bjmg-2019-0021>
 38. Ruella M, Salmoiraghi S, Rizzo A et al (2013) Telomere shortening in Ph-negative chronic myeloproliferative neoplasms: a biological marker of polycythemia vera and myelofibrosis, regardless of hydroxycarbamide therapy. *Exp Hematol* 41(7):627–634. <https://doi.org/10.1016/j.exphem.2013.03.007>
 39. Sacco M, Ranalli P, Lancellotti S et al (2020) Increased von Willebrand factor levels in polycythemia vera and phenotypic differences with essential thrombocythemia. *Res Pract Thromb Haemost* 4(3):413–421 Published 2020 Feb 28. <https://doi.org/10.1002/rth2.12315>
 40. Sazawal S, Singh K, Chhikara S, Chaubey R, Mahapatra M, Saxena R (2019) Influence of JAK2V617F allele burden on clinical phenotype of polycythemia vera patients: a study from India. *South Asian J Cancer* 8(2):127–129. https://doi.org/10.4103/sajc.sajc_161_18
 41. Silver RT, Vandris K, Wang YL et al (2011) JAK2(V617F) allele burden in polycythemia vera correlates with grade of myelofibrosis, but is not substantially affected by therapy. *Leuk Res* 35(2):177–182. <https://doi.org/10.1016/j.leukres.2010.06.017>
 42. Stein BL, Rademaker A, Spivak JL, Moliterno AR (2011) Gender and vascular complications in the JAK2 V617F-Positive myeloproliferative neoplasms. *Thrombosis* 2011:874146. <https://doi.org/10.1155/2011/874146>
 43. Stein BL, Saraf S, Sobol U et al (2013) Age-related differences in disease characteristics and clinical outcomes in polycythemia vera. *Leuk Lymphoma* 54(9):1989–1995. <https://doi.org/10.3109/10428194.2012.759656>
 44. Tefferi A, Strand JJ, Lasho TL et al (2007) Bone marrow JAK2V617F allele burden and clinical correlates in polycythemia vera. *Leukemia* 21(9):2074–2075. <https://doi.org/10.1038/sj.leu.2404724>
 45. Vannucchi AM, Antonioli E, Guglielmelli P et al (2007) Prospective identification of high-risk polycythemia vera patients based on JAK2(V617F) allele burden. *Leukemia* 21(9):1952–1959. <https://doi.org/10.1038/sj.leu.2404854>
 46. Vannucchi AM, Antonioli E, Guglielmelli P et al (2007) Clinical profile of homozygous JAK2 617V>F mutation in patients with polycythemia vera or essential thrombocythemia. *Blood* 110(3):840–846. <https://doi.org/10.1182/blood-2006-12-064287>
 47. Zhao S, Zhang X, Xu Y et al (2016) Impact of JAK2V617F mutation burden on Disease phenotype in Chinese patients with JAK2V617F-positive Polycythemia Vera (PV) and essential thrombocythemia (ET). *Int J Med Sci* 13(1):85–91 Published 2016 Jan 25. <https://doi.org/10.7150/ijms.10539>
 48. Zhou J, Ye Y, Zeng S et al (2013) Impact of JAK2 V617F mutation on hemogram variation in patients with non-reactive elevated platelet counts. *PLoS ONE* 8(2):e57856. <https://doi.org/10.1371/journal.pone.0057856>
 49. Guglielmelli P, Loscocco GG, Mannarelli C et al (2021) JAK2V617F variant allele frequency > 50% identifies patients with polycythemia vera at high risk for venous thrombosis. *Blood Cancer J* 11(12):199 Published 2021 Dec 11. <https://doi.org/10.1038/s41408-021-00581-6>
 50. Alvarez-Larrán A, Angona A, Ancochea A et al (2016) Masked polycythemia vera: presenting features, response to treatment and clinical outcomes. *Eur J Haematol* 96(1):83–89
 51. Alvarez-Larrán A, Senín A, Fernández-Rodríguez C et al (2017) Impact of genotype on leukaemic transformation in polycythemia vera and essential thrombocythemia. *Br J Haematol* 178(5):764–771. <https://doi.org/10.1111/bjh.14762>
 52. Ancochea A, Álvarez-Larrán A, Morales-Indiano C et al (2014) The role of serum erythropoietin level and jak2 v617f allele burden in the diagnosis of polycythemia vera. *Br J Haematol* 167(3):411–417
 53. Andersen CL, Bjørn ME, McMullin MF et al (2014) Circulating YKL-40 in patients with essential thrombocythemia and polycythemia vera treated with the novel histone deacetylase inhibitor vorinostat. *Leuk Res* 38(7):816–821
 54. Andréasson B, Pettersson H, Wasslavik C, Johansson P, Palmqvist L, Asp J (2020) ASXL1 mutations, previous vascular complications and age at diagnosis predict survival in 85 WHO-defined polycythemia vera patients. *Br J Haematol* 189(5):913–919
 55. Barbui T, Thiele J, Passamonti F et al (2012) Initial bone marrow reticulin fibrosis in polycythemia vera exerts an impact on clinical outcome. *Blood* 119(10):2239–2241
 56. Barbui T, Vannucchi AM, Finazzi G et al (2017) A reappraisal of the benefit-risk profile of hydroxyurea in polycythemia vera: a propensity-matched study. *Am J Hematol* 92(11):1131–1136
 57. Barosi G (2018) Spleen in myeloproliferative neoplasms. *Hemisphere* 2(Suppl 2):173–174 Published 2018 Jun 11. <https://doi.org/10.1097/HS9.000000000000115>
 58. Benati M, Montagnana M, Danese E et al (2015) Role of JAK2 V617F mutation and aberrant expression of microRNA-143 in myeloproliferative neoplasms. *Clin Chem Lab Med (CCLM)*. ;53(7)
 59. Benton CB, Boddu PC, DiNardo CD et al (2019) Janus kinase 2 variants associated with the transformation of myeloproliferative neoplasms into acute myeloid leukemia. *Cancer* 125(11):1855–1866. <https://doi.org/10.1002/cncr.31986>
 60. Bertozzi I, Bogoni G, Biagetti G et al (2017) Thromboses and hemorrhages are common in MPN patients with high JAK2V617F allele burden. *Ann Hematol* 96(8):1297–1302
 61. Borowczyk M, Wojtaszewska M, Lewandowski K et al (2015) The JAK2 V617F mutational status and allele burden may be related with the risk of venous thromboembolic events in patients

- with Philadelphia-negative myeloproliferative neoplasms. *Thromb Res* 135(2):272–280
62. Chang H, Shih L, Michelson AD et al (2013) Clinical and Laboratory significance of defective P2Y₁₂ pathway function in patients with myeloproliferative neoplasms: a pilot study. *Acta Haematol* 130(3):181–187
 63. Coltoff A, Mesa R, Gotlib J et al (2020) Real-world outcomes of Ruxolitinib Treatment for Polycythemia Vera. *Clin Lymphoma Myeloma Leuk* 20(10):697–703e1. <https://doi.org/10.1016/j.clml.2020.05.019>
 64. Crisà E, Cerrano M, Beggiato E et al (2017) Can pegylated interferon improve the outcome of polycythemia vera patients? *J Hematol Oncol* 10(1):15. <https://doi.org/10.1186/s13045-017-0395-1>. Published 2017 Jan 13
 65. Debureaux P, Cassinat B, Soret-Dulphy J et al (2020) Molecular profiling and risk classification of patients with myeloproliferative neoplasms and splanchnic vein thromboses. *Blood Adv* 4(15):3708–3715
 66. Gangaraju R, Song J, Kim SJ et al (2020) Thrombotic, inflammatory, and HIF-regulated genes and thrombosis risk in polycythemia vera and essential thrombocythemia. *Blood Adv* 4(6):1115–1130
 67. Garcia-Gisbert N, Fernández-Ibarrondo L, Fernández-Rodríguez C et al (2021) Circulating cell-free DNA improves the molecular characterisation of Ph-negative myeloproliferative neoplasms. *Br J Haematol* 192(2):300–309. <https://doi.org/10.1111/bjh.17087>
 68. Garcia-Gisbert N, Camacho L, Fernández-Ibarrondo L et al (2020) Analysis of saliva samples and cluster of differentiation 3 (CD3)+lymphocytes as a source of germline DNA in myeloproliferative neoplasms. *Br J Haematol* 189(5):e204–e207. <https://doi.org/10.1111/bjh.16624>
 69. Giona F, Teofili L, Moleti ML et al (2012) Thrombocythemia and polycythemia in patients younger than 20 years at diagnosis: clinical and biologic features, treatment, and long-term outcome. *Blood* 119(10):2219–2227
 70. Gupta V, Kennedy JA, Capo-Chichi JM et al (2021) Genetic factors rather than blast reduction determine outcomes of allogeneic HCT in BCR-ABL-negative MPN in blast phase [published correction appears in *Blood Adv*. ;5(11):2518]. *Blood Adv*. 2020;4(21):5562–5573. <https://doi.org/10.1182/bloodadvances.2020002727>
 71. Guru SA, Sumi MP, Mir R et al (2020) Ectopic PD-L1 expression in JAK2 (V617F) myeloproliferative neoplasm patients is mediated via increased activation of STAT3 and STAT5. *Hum Cell* 33(4):1099–1111
 72. Guy A, Danaee A, Paschalaki K et al (2020) Absence of JAK2V617F mutated endothelial colony-forming cells in patients with JAK2V617F myeloproliferative neoplasms and splanchnic vein thrombosis. *Hemasphere* 4(3):e364 Published 2020 May 5. <https://doi.org/10.1097/HS9.0000000000000364>
 73. Ha JS, Jeon DS, Kim JR, Ryou NH, Suh JS (2014) Analysis of the Ten-Eleven translocation 2 (TET2) gene mutation in myeloproliferative neoplasms. *Ann Clin Lab Sci* 44(2):173–179
 74. Heibl S, Gisslinger B, Jäger E et al (2020) Clinical, hematologic, biologic and molecular characteristics of patients with myeloproliferative neoplasms and a Chronic Myelomonocytic Leukemia-Like phenotype. *Cancers (Basel)* 12(7):1891
 75. Hussein K, Bock O, Theophile K et al (2009) JAK2(V617F) allele burden discriminates essential thrombocythemia from a subset of prefibrotic-stage primary myelofibrosis. *Exp Hematol* 37(10):1186–1193e7
 76. Karantanos T, Chaturvedi S, Braunstein EM et al (2020) Sex determines the presentation and outcomes in MPN and is related to sex-specific differences in the mutational burden. *Blood Adv* 4(12):2567–2576
 77. Kissova J, Ovesna P, Bulikova A, Zavřelova J, Penka M (2015) Increasing procoagulant activity of circulating microparticles in patients with Philadelphia-negative myeloproliferative neoplasms: a single-centre experience. *Blood Coagul Fibrinolysis* 26(4):448–453
 78. Kondo T, Okuno N, Naruse H et al (2008) Validation of the revised 2008 WHO diagnostic criteria in 75 suspected cases of myeloproliferative neoplasm. *Leuk Lymphoma* 49(9):1784–1791
 79. Koschmieder S, Chatain N (2018) Inflammation and anti-inflammatory approaches in myeloproliferative neoplasm. *Hemasphere* 2(Suppl 2):143–145 Published 2018 Jun 11. <https://doi.org/10.1097/HS9.0000000000000106>
 80. Kovacsovics-Bankowski M, Kelley TW, Efimova O et al (2015) Changes in peripheral blood lymphocytes in polycythemia vera and essential thrombocythemia patients treated with pegylated-interferon alpha and correlation with JAK2V617F allelic burden. *Exp Hematol Oncol* 5:28
 81. Kurtovic-Kozaric A, Islamagic E, Komic H et al (2020) The effects of mutational profiles on phenotypic presentation of myeloproliferative neoplasm subtypes in Bosnia: 18 year follow-up. *Bosn J Basic Med Sci* 20(2):236–247
 82. Larsen TS, Møller MB, de Stricker K et al (2009) Minimal residual disease and normalization of the bone marrow after long-term treatment with alpha-interferon2b in polycythemia vera. A report on molecular response patterns in seven patients in sustained complete hematological remission. *Hematology* 14(6):331–334
 83. Larsen TS, Pallisgaard N, Møller MB, Hasselbalch HC (2008) High prevalence of arterial thrombosis in JAK2 mutated essential thrombocythaemia: independence of the V617F allele burden. *Hematology* 13(2):71–76
 84. Larsen TS, Pallisgaard N, Møller MB, Hasselbalch HC (2008) Quantitative assessment of the JAK2 V617F allele burden: equivalent levels in peripheral blood and bone marrow. *Leukemia* 22(1):194–195
 85. Limvorapitak W, Parker J, Hughesman C, McNeil K, Foltz L, Karsan A (2020) No differences in outcomes between JAK2 V617F-Positive patients with variant allele fraction <2% versus 2–10%: a 6-Year Province-wide retrospective analysis. *Clin Lymphoma Myeloma Leuk* 20(9):e569–e578
 86. Luque Paz D, Chauveau A, Boyer F et al (2017) Sequential analysis of 18 genes in polycythemia vera and essential thrombocythemia reveals an association between mutational status and clinical outcome. *Genes Chromosomes Cancer* 56(5):354–362
 87. Lussana F, Carobbio A, Salmoiraghi S et al (2017) Driver mutations (JAK2V617F, MPLW515L/K or CALR), pentraxin-3 and C-reactive protein in essential thrombocythemia and polycythemia vera. *J Hematol Oncol* 10(1):54
 88. Makarik TV, Abdullaev AO, Nikulina EE et al (2021) Low JAK2 V617F allele Burden in Ph-Negative chronic myeloproliferative neoplasms is Associated with additional CALR or MPL gene mutations. *Genes (Basel)* 12(4):559
 89. Mattar MM, Nassef S, El Husseiny NM et al (2019) Incidence of silent thrombosis in patients younger than 60 years with myeloproliferative neoplasms: single-center Egyptian study. *Clin Lymphoma Myeloma Leuk* 19(8):e425–e429
 90. Mattar MM, Morad MA, El Husseiny NM, Ali NH, El Demerdash DM (2016) Correlation between JAK2 allele burden and pulmonary arterial hypertension and hematological parameters in Philadelphia negative JAK2 positive myeloproliferative neoplasms. An Egyptian experience. *Ann Hematol* 95(10):1611–1616
 91. Milosevic Feenstra JD, Jäger R, Schischlik F et al (2022) PD-L1 overexpression correlates with JAK2-V617F mutational burden and is associated with 9p uniparental disomy in myeloproliferative neoplasms. *Am J Hematol* 97(4):390–400
 92. Misawa K, Yasuda H, Araki M et al (2018) Mutational subtypes of JAK2 and CALR correlate with different clinical features in

- Japanese patients with myeloproliferative neoplasms. *Int J Hematol* 107(6):673–680
93. Moia R, Cittone MG, Boggione P et al (2021) Stiffer spleen predicts higher bone marrow fibrosis and higher JAK2 allele Burden in patients with myeloproliferative neoplasms. *Front Oncol* 11:777730
 94. Nangalia J, Bench AJ, Green AR, Godfrey AL (2019) Myeloproliferative neoplasms. In *Molecular Hematology* (eds D. Provan and J. Gribben). <https://doi.org/10.1002/9781119252863.ch7>
 95. Ok CY, Trowell KT, Parker KG et al (2021) Chronic myeloid neoplasms harboring concomitant mutations in myeloproliferative neoplasm driver genes (JAK2/MPL/CALR) and SF3B1. *Mod Pathol* 34(1):20–31. <https://doi.org/10.1038/s41379-020-0624-y>
 96. Panova-Noeva M, Marchetti M, Spronk HM et al (2011) Platelet-induced thrombin generation by the calibrated automated thrombogram assay is increased in patients with essential thrombocythemia and polycythemia vera. *Am J Hematol* 86(4):337–342
 97. Park SH, Chi HS, Cho YU, Jang S, Park CJ (2013) The allele burden of JAK2 V617F can aid in differential diagnosis of Philadelphia chromosome-negative myeloproliferative neoplasm. *Blood Res* 48(2):128–132
 98. Pearson S, Blance R, Somervaille TCP, Whetton AD, Pierce A (2019) AXL Inhibition extinguishes primitive JAK2 mutated myeloproliferative neoplasm progenitor cells. *Hemasphere* 3(3):e233 Published 2019 Jun 4. <https://doi.org/10.1097/H59.0000000000000233>
 99. Perricone M, Polverelli N, Martinelli G et al (2017) The relevance of a low JAK2V617F allele burden in clinical practice: a monocentric study. *Oncotarget* 8(23):37239–37249
 100. Randi ML, Ruzzon E, Tezza F et al (2011) JAK2V617F mutation is common in old patients with polycythemia vera and essential thrombocythemia. *Aging Clin Exp Res* 23(1):17–21
 101. Risum M, Madelung A, Bondo H et al (2011) The JAK2V617F allele burden and STAT3- and STAT5 phosphorylation in myeloproliferative neoplasms: early prefibrotic myelofibrosis compared with essential thrombocythemia, polycythemia vera and myelofibrosis. *APMIS* 119(8):498–504
 102. Rotunno G, Pacilli A, Artusi V et al (2016) Epidemiology and clinical relevance of mutations in postpolycythemia vera and postessential thrombocythemia myelofibrosis: a study on 359 patients of the AGIMM group. *Am J Hematol* 91(7):681–686
 103. Sant'Antonio E, Guglielmelli P, Pieri L et al (2020) Splanchnic vein thromboses associated with myeloproliferative neoplasms: an international, retrospective study on 518 cases. *Am J Hematol* 95(2):156–166
 104. Schischlik F, Jäger R, Rosebrock F et al (2019) Mutational landscape of the transcriptome offers putative targets for immunotherapy of myeloproliferative neoplasms. *Blood* 134(2):199–210. <https://doi.org/10.1182/blood.2019000519>
 105. Schino M, Fiorentino V, Rossi E et al (2021) Bone marrow megakaryocytic activation predicts fibrotic evolution of Philadelphia-negative myeloproliferative neoplasms. *Haematologica* 106(12):3162–3169
 106. Shirane S, Araki M, Morishita S et al (2015) Consequences of the JAK2V617F allele burden for the prediction of transformation into myelofibrosis from polycythemia vera and essential thrombocythemia. *Int J Hematol* 101(2):148–153
 107. Singdong R, Siriboonpiputtana T, Chareonsirisuthigul T et al (2016) Characterization and prognosis significance of JAK2 (V617F), MPL, and CALR mutations in Philadelphia-Negative myeloproliferative neoplasms. *Asian Pac J Cancer Prev* 17(10):4647–4653
 108. Soderquist CR, Ewalt MD, Czuchlewski DR et al (2018) Myeloproliferative neoplasms with concurrent BCR-ABL1 translocation and JAK2 V617F mutation: a multi-institutional study from the bone marrow pathology group. *Mod Pathol* 31(5):690–704. <https://doi.org/10.1038/modpathol.2017.182>
 109. Sørensen AL, Bjørn ME, Riley CH et al (2019) B-cell frequencies and immunoregulatory phenotypes in myeloproliferative neoplasms: influence of ruxolitinib, interferon- α 2, or combination treatment. *Eur J Haematol* 103(4):351–361
 110. Sørensen AL, Knudsen TA, Skov V et al (2021) Smoking impairs molecular response, and reduces overall survival in patients with chronic myeloproliferative neoplasms: a retrospective cohort study. *Br J Haematol* 193(1):83–92. <https://doi.org/10.1111/bjh.17130>
 111. Soudet S, Le Roy G, Cadet E et al (2022) JAK2 allele burden is correlated with a risk of venous but not arterial thrombosis. *Thromb Res* 211:1–5
 112. Spivak JL, Considine M, Williams DM et al (2014) Two clinical phenotypes in polycythemia vera. *N Engl J Med* 371(9):808–817
 113. Stein BL, Rademaker A, Spivak JL, Moliterno AR (2011) Gender and vascular complications in the JAK2 V617F-Positive myeloproliferative neoplasms. *Thrombosis* 2011:874146
 114. Tefferi A, Sirhan S, Lasho TL et al (2005) Concomitant neutrophil JAK2V617F mutation screening and PRV-1 expression analysis in myeloproliferative disorders and secondary polycythemia. *Br J Haematol* 131(2):166–171
 115. Trifa AP, Bănescu C, Voinea CM et al (2018) Modest contribution of JAK2 V617F allele burden to the occurrence of major thrombosis in polycythemia vera and essential thrombocythemia. *Blood Cells Mol Dis* 73:45–46
 116. Trifa AP, Cucuianu A, Petrov L et al (2010) The G allele of the JAK2 rs10974944 SNP, part of JAK2 46/1 haplotype, is strongly associated with JAK2 V617F-positive myeloproliferative neoplasms. *Ann Hematol* 89(10):979–983
 117. Utke Rank C, Weis Bjerrum O, Larsen TS et al (2016) Minimal residual disease after long-term interferon- α 2 treatment: a report on hematological, molecular and histomorphological response patterns in 10 patients with essential thrombocythemia and polycythemia vera. *Leuk Lymphoma* 57(2):348–354
 118. Vadikolia C, Tsatalas C, Anagnostopoulos K et al (2011) Proteolytic matrix metalloproteinases and inhibitors in BCR-ABL1-Negative myeloproliferative neoplasms: correlation with JAK2^{V617F} mutation status. *Acta Haematol* 126(1):54–62
 119. Yang N, Park S, Cho M et al (2018) GATA1 expression in BCR/ABL1-negative myeloproliferative neoplasms. *Ann Lab Med* 38(4):296–305
 120. Yoo E, Park K, Won H et al (2016) Genetic characteristics of Polycythemia Vera and essential thrombocythemia in Korean patients. *Clin Lab Anal* 30(6):1061–1070
 121. Zangari M, Fink L, Tolomelli G et al (2013) Could hypoxia increase the prevalence of thrombotic complications in polycythemia vera? *Blood Coagul Fibrinolysis* 24(3):311–316
 122. Zhang Y, Zhou Y, Wang Y et al (2020) Thrombosis among 1537 patients with JAK2V617F-mutated myeloproliferative neoplasms: risk factors and development of a predictive model. *Cancer Med* 9(6):2096–2105
 123. Ianotto JC, Chauveau A, Boyer-Perrard F et al (2018) Benefits and pitfalls of pegylated interferon- α 2a therapy in patients with myeloproliferative neoplasm-associated myelofibrosis: a French Intergroup of Myeloproliferative neoplasms (FIM) study. *Haematologica* 103(3):438–446. <https://doi.org/10.3324/haematol.2017.181297>
 124. Kiladjian JJ, Klade C, Georgiev P et al (2022) Long-term outcomes of polycythemia vera patients treated with ropeginterferon Alfa-2b. *Leukemia* 36(5):1408–1411. <https://doi.org/10.1038/s41375-022-01528-x>
 125. de Oliveira RD, Soret Dulphy J, Zhao LP et al (2020) Interferon-Alpha (IFN) Therapy discontinuation is feasible in

- Myeloproliferative Neoplasm (MPN) patients with complete hematological remission. *Blood* 136:S1:35–36. <https://doi.org/10.1182/blood-2020-141223>
126. Harrison CN, Nangalia J, Boucher R et al (2023) Ruxolitinib Versus Best available therapy for Polycythemia Vera intolerant or resistant to Hydroxycarbamide in a Randomized Trial. *J Clin Oncol* 41(19):3534–3544. <https://doi.org/10.1200/JCO.22.01935>
127. Gisslinger H, Klade C, Georgiev P et al (2023) Event-free survival in patients with polycythemia vera treated with ropeginterferon alfa-2b versus best available treatment. *Leukemia* 37(10):2129–2132. <https://doi.org/10.1038/s41375-023-02008-6>
128. Moliterno AR, Kaizer H, Reeves BN (2023) JAK2 V617F allele burden in polycythemia vera: burden of proof. *Blood* 141(16):1934–1942. <https://doi.org/10.1182/blood.2022017697>
129. Mesa RA, Miller CB, Thyne M et al (2017) Differences in treatment goals and perception of symptom burden between patients with myeloproliferative neoplasms (MPNs) and hematologists/oncologists in the United States: findings from the MPN Landmark survey. *Cancer* 123(3):449–458. <https://doi.org/10.1002/cncr.30325>
130. Tsai TH, Yu LH, Yu MS et al (2023) Real-world patient characteristics and treatment patterns of polycythemia vera in Taiwan between 2016 and 2017: a nationwide cross-sectional study. *Ther Adv Hematol* 14:20406207231179331 Published 2023 Jun 15. <https://doi.org/10.1177/20406207231179331>
131. Parasuraman S, Yu J, Paranagama D et al (2018) Cytoreductive treatment patterns among US veterans with polycythemia vera. *BMC Cancer* 18:528–018

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