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Preserving thrombosis and life years in polycythemia vera: start by reading the biology of the disease

Running heads: *Preserving thrombosis and life years in PV*

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TB, AG, AC, MS contributed to the conceptualization of this Perspective and to the literature review. TB wrote the original draft that was approved by all authors.

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Abstract

The Swedish nationwide study by Leontyeva *et al. (Haematologica, sept, 2025)* revealed that patients with myeloproliferative neoplasms (MPN) continue to lose life years compared with the general population, with polycythemia vera (PV) showing a 1.8-year loss in restricted mean survival at 15 years. Despite being classified as "low risk," these younger patients lose more life years relative to age-matched peers. They face decades of exposure to clonal proliferation, inflammation, and thromboinflammation, which contribute to vascular injury, myelofibrosis, and secondary cancers.

Evidence suggests that early, biology-guided therapy may modify this trajectory. Interferon, particularly ropeginterferon alfa-2b, and ruxolitinib reduces *JAK2*^{V617F} allele burden, systemic inflammation, as reflected by the neutrophil-to-lymphocyte ratio (NLR), and thrombosis rates, demonstrating long-term disease-modifying potential. The challenge lies in identifying which younger patients should receive cytoreductive therapy, as these treatments, while effective, may be poorly tolerated or burdensome over decades. Biological markers such as persistent leukocytosis, elevated NLR, rising *JAK2*^{V617F} variant allele frequency, or high phlebotomy burden can guide treatment decisions more precisely than age alone. Tailoring therapy in younger PV patients according to disease biology and individual tolerance may prevent irreversible complications, improve quality of life, and ultimately reduce the years of life lost.

Introduction

The recent Swedish study by Leontyeva *et al.*[1], draws attention to an important and still unresolved issue. Using a nationwide cohort and advanced statistical methods, the authors demonstrated that young patients with myeloproliferative neoplasms (MPN) have a shorter life expectancy than the general population. For polycythemia vera (PV), the loss in restricted mean survival time over 15 years is about 1.8 years, while across all MPNs it reaches approximately 4.3 years. The study also provides sex-specific survival curves, showing that men and women have different background life expectancies and, in some cases, different excess mortality rates. As a result, the absolute years of life lost (LLE) can differ by sex even when hazard ratios are similar. These findings shift the focus from short-term hematologic targets to what truly matters to patients: preserving life years. Interestingly, Leontyeva et al. pointed out that women and men do not lose the same number of years at a given age due to differences in background life expectancy; the same hazard ratio can represent a greater number of years at risk for women.[1] In PV, sex differences in outcomes vary by series, but younger women may experience more unusual-site venous events (e.g. splanchnic or cerebral), for which aspirin alone is inadequate. In this context, inherited and environmental contributors to thrombosis and, in young women, the added risks posed by hormonal contraceptives and pregnancy should also be considered. Therefore, it is reasonable to keep biological thresholds identical for both sexes and to provide sex-specific counselling regarding pregnancy planning, iron deficiency resulting from phlebotomy and proactive management of venous risk.

This study prompted us to reflect not only on the loss of life years among patients under 60 years of age but also on the biological and clinical factors that may shorten survival in this population. Younger patients with PV warrant special attention because, although often labeled as "low risk" by ELN (European Leukemia Net) criteria, they lose more years of life relative to age-matched peers and it remains uncertain whether they require distinct thrombotic risk stratification. The paradox lies in the fact that these patients, while free of prior thrombosis and under 40-60, face prolonged exposure to clonal proliferation, inflammation, and thromboinflammatory injury, processes that promote vascular damage, myelofibrosis, and secondary cancers[2–4]. Since younger individuals have naturally longer life expectancy, even modest excess mortality translates into significant years of life lost.

Current risk stratification therefore underestimates the true biological hazard in these patients. A purely age-based definition of "low risk" may delay disease-modifying therapy in those who, based on their biological profile, would benefit most. A proactive management approach for selected younger patients is thus biologically and clinically justified and may be crucial for preserving long-term survival and quality of life.

In this Perspective, we aim to explore how best to reduce excess mortality in young patients with PV and to define the most meaningful therapeutic endpoints for this population, considering not only short-term toxicity but also the potential long-term consequences of treatment. To achieve this, we integrate recent epidemiologic and biological evidence with our own interpretation, with the goal of stimulating a broader discussion on how to minimize years of life lost in PV. Our intention is to connect population-level observations, such as those emerging from the Swedish nationwide study, with mechanistic

insights and evolving therapeutic data, ultimately proposing a forward-looking framework to guide clinical decision-making and inform the design of future trials in younger patients with PV.

Why Young Patients with Polycythemia Vera Require a Different Perspective

Regardless of age, thrombosis remains a defining feature of PV. Real-world data show that even very young patients (≤25 years) have a substantial thrombotic burden: 21.5% present with prior thrombosis at diagnosis and 16.3% experience recurrence during follow-up.[5] The pattern, however, differs from older patients—young individuals show a higher proportion of venous events, including splanchnic and other unusual sites, whereas arterial events are less common due to the absence of traditional cardiovascular risk factors. The mechanisms underlying venous thrombosis remain unclear but may involve chronic inflammation, as young PV patients also display elevated inflammatory cytokines compared with the general population. These inflammatory pathways contribute not only to thrombosis but also to symptom burden: fatigue, microvascular disturbances, and impaired quality of life may be particularly impactful in this age group, given interruptions to education, career development, family planning, and social participation.[6]

Moreover, as pointed out by Leontyeva et al.[1] when compared with age-matched controls in the general population, younger individuals with PV experience a disproportionately greater excess mortality and lose more years of life. This long-term attrition reflects the cumulative incidence of complications—including recurrent thrombosis, progression to myelofibrosis or acute leukemia, and second malignancies—occurring over decades of disease. Together, these patients have unique vulnerabilities and require therapeutic strategies that look beyond short-term hematocrit control and aim instead to modify the long-term natural history of the disease.

Evidence That Early Intervention May Preserve Complications and Life Years

A key question is whether there is evidence to support early pharmacological intervention in order to reduce years of life lost and prevent major complications such as thrombosis and the evolution of the disease into myelofibrosis (MF), as well as the development of solid tumors in younger patients with MPN, particularly PV. Recent observational studies have addressed this issue.

Abu-Zeinah et al.[2] demonstrated that patients diagnosed at a younger age experience higher excess mortality than older patients compared to their age-matched peers. In line with the findings of Leontyeva et al.,[1] these younger patients experience a greater loss of relative survival time, although younger individuals with PV, ET or PMF who are <60 years will still live longer in absolute terms. This pattern was observed across all MPN subtypes, being most pronounced in PV and PMF, where there is excess cardiovascular and cancer-related mortality. Their findings show that younger patients are vulnerable to the cumulative consequences of decades of chronic inflammation if they do not receive adequate treatment.

Drawing on their prior work, these authors showed that interferon-α emerges as the only therapy consistently associated with reduced MF progression, cancer-related mortality, and potential restoration of near-normal life expectancy in PV[7]. They argued that age alone should not delay the implementation

of disease-modifying strategies or prevent younger patients from accessing timely therapy or participating in clinical trials.

Reports in adolescents and young adults (AYAs) showed that thrombosis can develop at an early stage and that progression to myelofibrosis or acute leukemia is not uncommon.[5] In these younger individuals, the biology of the disease also differs: in essential thrombocythemia (ET) triple-negative cases are more prevalent, inflammatory cytokine levels are higher and the mutational load is smaller than in older adults. These findings suggest that young patients should not simply be reassured because they are "low risk" according to adult criteria. Treatment should be tailored to the individual and interferon should be considered at an earlier stage if biological risk is evident. Hydroxyurea (HU) remains an option when interferon is not tolerated or contraindicated. Current data suggest that, for long-term goals, interferon-based drugs are the preferred first-line option in line with ELN.

In the largest series of AYAs with ET or PV (aged <25 years; n = 348), the thrombotic rate was approximately 1.9 per 100 patient-years, which is similar to that observed in older cohorts.[6] Standard adult risk scores did not predict thrombosis; instead, leukocytosis (>11×10^9/L) was the main predictor. Progression to myelofibrosis in ET occurred at a rate of ~0.7 per 100 patient-years and was associated with *CALR* mutations and prior thrombosis.[5] Importantly, first-line interferon therapy was associated with improved myelofibrosis-free survival and no progression was observed in patients who started treatment with interferon.[6]

The above-mentioned studies were observational in nature but consistently support the use of interferon as first-line choice in young people with PV, whose favorable efficacy has been demonstrated in randomised clinical trials. In the PROUD/CONTINUATION-PV trial[8], pegylated interferon alfa-2b was compared with hydroxyurea and showed higher complete haematologic response rates, a greater reduction in *JAK2*^{V617F} variant allele frequency, and significant improvement in event-free survival. A smaller Phase III trial similarly demonstrated that pegylated IFN-α2a was superior to hydroxyurea in reducing the *JAK2*^{V617F} allele burden but was equally efficacious to hydroxyurea in terms of hematological response. [9]

In addition, evidence supporting early use of interferon in younger, low-risk patients derives from the Low-PV Phase II randomised trial[10–12]. In this study, younger PV patients classified as low risk for thrombosis according to ELN criteria were randomly assigned to low-dose ropeginterferon alfa-2b (100 µg every 2 weeks) versus phlebotomy. At 12–24 months, ropeginterferon provided superior disease control, maintaining haematocrit ≤45% without disease progression more effectively than phlebotomy, reducing the need for additional phlebotomies, improving symptoms, and achieving partial molecular responses in ~55% of patients (defined as >50% reduction in *JAK2*^{V617F} VAF). Among those who remained on treatment, the primary endpoint was sustained in 97%, 94%, and 94% at years 3, 4, and 5, respectively, with 60% of patients remaining phlebotomy-free. Notably, an early high phlebotomy requirement (>3 in 6 months) predicted failure of phlebotomy-only management, suggesting to transition to IFN. Thus, in young, low-risk PV patients, low-dose peg-IFN alfa 2b offers clear advantages over phlebotomy-based approaches, delivering superior hematologic control, fewer phlebotomies, meaningful molecular responses, and durable long-term efficacy with an acceptable safety profile.

It is noteworthy that a favorable response to interferon has been found to depend on clonal tumor burden and the benefit appears greater when treatment is started early, before the mutant clone has had time to expand, as is typically seen in low-risk PV cases.[8] In patients with PV who did not receive IFN in the early phase of the disease, *JAK2*^{V617F} VAF approximately doubles every 1.4 years. Conversely, most responders to IFN showed a steady reduction in clone size; some experienced a gradual decline (half-life ~1.6 years), whereas many exhibited a two-phase decline with a faster long-term reduction indicating later but more sustained responses.

A low starting dose with gradual titration to achieve complete hematologic response is advised. Once a stable response is achieved, dose reduction may be appropriate, and treatment discontinuation can be considered in patients who maintain a deep molecular response (*JAK2*^{V617F} VAF <10%) for at least two years.[13]

Although profound, durable reductions in *JAK2*^{V617F} allele burden appear clinically meaningful, and the neutrophil-to-lymphocyte ratio (NLR) may serve as a practical surrogate of *JAK2* suppression,[14,15] there are still no standardized recommendations on monitoring VAF or determining when IFN therapy can be safely discontinued. [13]

While peg-interferon alfa-2a and alfa-2b have a well-established safety profile in the short- and medium-term, patients—especially younger individuals—should be informed that long-term safety data are still accumulating. This uncertainty should be incorporated into shared decision-making. A thorough baseline eligibility assessment is recommended to ensure safe use. Typically, this includes evaluation of mental health history, screening for autoimmune disorders, thyroid function testing, and routine liver and kidney function tests to identify patients who may require closer monitoring.

Unfortunately, some patients do not respond to the drug or are intolerant of it, and therefore require an individualized approach. Options include dose adjustment or switching to alternative agents such as hydroxyurea or ruxolitinib, particularly if a thrombotic event occurs during interferon therapy. Evidence from the RESPONSE trials[16] and real-world cohorts—including patients previously exposed to interferon—shows that ruxolitinib provides durable hematocrit and symptom control with predictable tolerability. Short-term toxicity mainly involves manageable cytopenias and mild infections, while long-term safety remains stable, with no excess leukemic progression but a recognized need for dermatologic and herpes-zoster surveillance.

Unlike hydroxyurea and other cytoreductive therapies that have historically raised concerns about leukemogenic potential, long-term follow-up of patients treated with interferon has not demonstrated an increased risk of leukemic transformation. Recent reviews emphasize that interferon maintains a favorable long-term safety profile, with no evidence to support a leukemogenic effect or an excess of secondary cancers. Together, these data reinforce the view that interferon may represent a safer long-term therapeutic option with respect to both leukemogenesis.[13] Additionally, emerging data suggest that intermittent or de-escalated interferon dosing strategies may be feasible, potentially improving tolerability and cost-efficiency without compromising disease control.

With regard to cost, two studies have specifically addressed this issue and calculated that interferon, particularly ropeginterferon alfa-2b, is a cost-effective treatment option for patients with PV when assessed over long time horizons.[17,18] Both U.S. and European analyses conclude that, despite higher upfront drug costs, the long-term clinical benefits—reduced need for phlebotomy, improved haematologic control, and potential disease-modifying effects—justify its overall economic value.

Two biologically promising agents—Bomedemstat (LSD1 inhibitor)[19] and Givinostat (HDAC inhibitor, FDA fast-tracked in May 2025)[20] —are under evaluation but concerns about toxicity remain central to defining their role in younger patients.

Does Preventing Vascular Complications Attenuate PV Disease Evolution and losing years of life?

Thrombosis is a leading cause of death in polycythemia vera (PV), accounting for roughly one-third of all fatalities.[21] Preventing vascular complications may not only avert catastrophic organ damage but also attenuate disease evolution that manifests decades after diagnosis. Thrombosis, inflammation, and PV progression are increasingly understood as components of a self-reinforcing biological circuit.

Vascular events are not isolated clinical accidents, but rather manifestations of a chronic inflammatory environment driven by *JAK2*^{V617F}.[22,23] Each thrombotic or atherosclerotic episode amplifies IL-1β, TNF and NF-κB signaling, thereby reinforcing neutrophil activation, neutrophil extracellular trap (NET) formation and platelet–leukocyte interaction.[24–28] This inflammatory amplification increases the likelihood of recurrent thrombosis and fosters a bone marrow environment conducive to fibrosis and clonal expansion. Therefore, interrupting this cycle by preventing vascular events may represent a genuine disease-modifying intervention.[23,29,30]

Several clinical and biological observations support this view. Elevated leukocyte counts, a high neutrophil-to-lymphocyte ratio (NLR) and increased C-reactive protein, markers of systemic inflammation, are strongly associated with both thrombosis and progression to myelofibrosis or leukaemia.[31,32] Therapies that normalize these parameters, are associated with improved event-free survival. The early use of interferon not only prevents vascular complications, but may also reduce the *JAK2*^{V617F} allele burden, but is hypothesized to limit the emergence of additional clones that drive disease evolution; however, definitive proof of this effect is not yet available and current evidence is largely observational.

Preventing thrombotic events also preserves organ integrity. Arterial and venous thromboses often lead to irreversible damage to the heart, brain, liver, or other organs, each of which contributes to premature death, regardless of haematological control.[33,34] Therefore, avoiding these complications extends survival by reducing immediate mortality and preventing long-term organ failure and disability. Furthermore, minimizing phlebotomy reduces iron deficiency and secondary thrombocytosis, which can exacerbate microvascular ischaemia, fatigue and predispose to major thrombosis.

An increasing amount of evidence is documenting that thrombosis can also be associated with a higher risk of solid tumours in the general population.[35]

In a multistate analysis of 1,545 PV patients, incident thrombosis, mainly arterial, was associated with earlier progression to post-PV myelofibrosis and increased mortality.[36] In the REVEAL study, a history of thrombosis predicted subsequent MF progression and death, alongside longer disease duration and leukocytosis.[34]

A multicenter nested case–control study of MPNs showed that post-diagnosis thrombosis may predict the development of solid tumours later in life.[37,38] Among the source cohort, 647 patients who developed a second solid cancer (cases) were each matched with two MPN controls without cancer (n = 1,234). The primary exposure was incident thrombosis after MPN diagnosis, analyzed separately as arterial or venous/splanchnic. The outcomes were overall carcinoma and, in a parallel analysis, non-melanoma skin cancer whose frequency was significantly and independently higher after HU or ruxolitinib. Incident arterial thrombosis was independently associated with subsequent carcinoma using multivariable conditional logistic regression (OR 1.97; 95% CI 1.14–3.41; p=0.015), whereas venous thrombosis was not (OR 1.03; 95% CI 0.58–1.82). Interestingly, aspirin use was associated with a lower risk of carcinoma (OR 0.64; 95% CI 0.47–0.87), whereas hydroxyurea use was associated with a higher risk of non-melanoma skin cancer (OR 2.08; 95% CI 1.09–3.98).[38] The median timing of arterial events was approximately 4 years before cancer occurrence. An age-stratified analysis revealed that the arterial-then-cancer sequence was an independent predictor, particularly in patients under 60 years of age.[4] The study has limitations, including its retrospective design and potential confounding by indication. However, the results support a mechanistic link between arterial immunothrombosis, chronic inflammation and oncogenesis, suggesting the need for earlier anti-inflammatory and cytoreductive strategies.

Similar patterns were observed outside MPN, where myocardial infarction, stroke, and limb ischemia often precede solid tumors, suggest shared biological pathways, including chronic inflammation, oxidative stress, metabolic dysfunction, microbial dysbiosis, CHIP, hormonal factors, and cellular senescence, with inflammation playing a central role.[39–41]

Supporting this link, the CANTOS trial, the largest study of cytokine inhibition, demonstrated that IL-1β blockade not only reduced cardiovascular events but also decreased lung cancer incidence and cancer-related mortality.[42] These findings highlight the convergence of IL-1β biology in thrombosis and cancer and the potential of IL-1β–targeted therapy to address both.[43]

Taken together, the current evidence suggests that preventing vascular complications could affect the long-term course of PV by stopping the *JAK2*-driven clonal disease and the cycle of inflammation and thrombosis. The associations between thrombosis, myelofibrosis progression, and cancer risk are biologically plausible and consistent with the central role of chronic inflammation, as previously mentioned. However, as these observations are largely derived from retrospective analyses and observational cohorts, they require confirmation in prospective studies specifically designed to evaluate disease evolution and long-term outcomes. They should therefore be considered provisional until validated by additional clinical evidence.

How to Recognize the Aggressive Biology of PV

Recognizing and monitoring the biological activity of PV is key to identifying patients at risk of progression and determining when to initiate disease-modifying therapy.[44,45] Biological activity reflects the combined effects of clonal proliferation, inflammatory activation, and immune dysregulation, which together drive vascular injury, fibrosis, and reduced survival.[46] *JAK2*^{V617F} remains the defining molecular hallmark of PV and best surrogate for disease burden, as demonstrated in both randomized clinical trials and observational studies. Rising *JAK2*^{V617F} VAF is linked to thrombosis, clonal expansion, and myelofibrosis, while its reduction with interferon, ruxolitinib, or transplantation correlates with event-free-survival and fewer vascular events. Non-driver mutations (*TET2*, *DNMT3A*, *ASXL1*) refine prognosis[47] and modulate therapy response but do not replace *JAK2*^{V617F} as the principal biological marker.[48]

Inflammation lies at the heart of MPN biology, and the neutrophil-to-lymphocyte ratio (NLR) provides a simple and consistent insight into it. The *JAK2*^{V617F} mutation increases the number of myeloid cells while reducing the number of lymphoid cells, naturally driving the NLR up, so a high NLR often signals both systemic inflammation and a more aggressive clone.[49] In PV, patients with a baseline NLR of at least 3.5 have a longer disease duration, greater splenomegaly, a higher *JAK2*^{V617F} allele burden and more classic hyperproliferative features than those with an NLR below 3.5.[14] Treatment matters: ropeginterferon substantially lowers the NLR, particularly in patients with a high baseline NLR, and its decline closely tracks reductions in *JAK2*^{V617F}, linking inflammatory control to clonal suppression.[14] Across PROUD/CONTINUATION-PV, ropeginterferon produced deeper NLR reductions over 60 months than hydroxyurea (HU), the effect of which waned and which does not meaningfully lower *JAK2* burden.[15,50] In ECLAP, propensity-matched HU versus phlebotomy showed no meaningful fall in NLR at 12 months, highlighting HU's limited anti-inflammatory impact.[15] From a clinical perspective, NLR carries significant prognostic value: time-dependent analyses demonstrate that an NLR of ≥3.3 is associated with an increased risk of total thrombosis, whereas leukocytosis loses significance.[15] Furthermore, sustained reductions in NLR are associated with improved event-free survival. Joint models confirm that a one-unit increase in NLR is associated with a ~10% higher risk of thrombosis and death, independently of age, HU use, or cardiovascular factors.[15] Recognizing heightened biological activity, through rising VAF, persistent leukocytosis, or elevated NLR, should prompt early intervention. By controlling this biological sequence early, especially in younger patients, vascular injury prevented, disease evolution delayed or avoided and survival may be preserved.[7]

Of note, in line with what seen with Ropeginterferon alfa 2b, PV patients resistant/intolerant to HU with high NLR had elevated white blood cell counts, increased neutrophils, reduced lymphocytes, and significantly higher *JAK2*^{V617F} VAF. Importantly, under ruxolitinib treatment, only the high-NLR group showed a marked and sustained reduction in NLR, primarily driven by a selective decrease in neutrophils.[51] This was paralleled by a significant decline in *JAK2*^{V617F} VAF.
Similar results were reported in the MAJIC study[52] indicating that ruxolitinib response is linked to prolonged event free, progression free and overall survival in HU resistant PV patients. However, in this latter trial NLR was not examined in relationship with the suppression of *JAK2* or event-free survival.

Overall, NLR emerged as a simple yet powerful biomarker reflecting both clonal and inflammatory dynamics, especially in patients starting therapy with higher NLR values.
The potential utility of NLR also emerged from data indicating a large cardiovascular prevention in the general population. IL-1β blockade with canakinumab, a monoclonal antibody targeting IL-1β, is one of the interventions capable of lowering NLR by reducing neutrophil levels while sparing lymphocytes.[43] Since IL-1β signaling plays a central role in *JAK2*-driven hematopoiesis and inflammation, anti–IL-1β monoclonal antibodies could be considered as a rational adjunct to cytoreductive drugs. Such combination therapies could provide a targeted approach to modulate the inflammatory axis without compromising lymphocyte-mediated immune surveillance, an important finding particularly for younger patients.

Conclusion and Future Perspective

Although younger patients with PV live longer in absolute terms than older patients, they still lose measurable years of life compared with their peers. This reflects the biology of a proliferative and inflammatory disease rather than aging itself. Stable disease may warrant observation, but once biological activity emerges, early cytoreductive therapy should be considered. Meaningful progress in reducing life years lost will depend on moving beyond traditional, age-based risk models toward biology-driven, and potentially sex-informed, treatment strategies. Future prospective trials should test whether early, biology-guided interventions can prevent vascular injury, delay progression, and improve survival.

Ultimately, reducing the years of life lost in PV will require translating disease biology into everyday clinical practice, shifting the focus from conventional hematologic control to strategies that truly extend life expectancy by preventing vascular injury and delaying disease progression while posing no major safety risks.

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