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CORRESPONDENCE

Why *JAK2*-mutated neutrophils deserve to be on center stage in polycythemia vera

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To The Editor

In polycythemia vera (PV), an increased neutrophil-to-lymphocyte ratio (NLR) is a risk factor for venous thrombosis [1]. Recent studies showed that reductions in the NLR correlated with suppression of *JAK2*^{V617F} variant-allele frequency (VAF) and were associated with improved event-free survival (EFS) in PV [2, 3]. It is likely that similar correlations also exist in essential thrombocythemia (ET), although there is limited published data of the impact of NLR on EFS and thromboses in ET. The results imply that NLR may be more than just a generic inflammatory marker, but rather a dynamic surrogate of clonal activity and prognosis in PV with therapeutic implications, particularly for interferon (IFN)-based strategies.

Despite its ubiquity and low cost, NLR has been relatively neglected in PV risk assessment compared with hematocrit and platelet counts. The emerging evidence base endorses leukocyte-based metrics as a powerful biomarker for disease related burden and risk; in ECLAP and other cohorts, higher NLR was associated with venous thrombosis and mortality in PV [2, 3]. Notably, contemporary analyses from the prospective REVEAL study identified sustained leukocytosis as an independent risk factor for thrombotic events even when hematocrit target was attained, underscoring that "white cells matter" in day-to-day practice [4]. This emphasizes the observation that therapies differ in their capacity to normalize NLR and, by extension, to modulate risk.

We believe the clinical relevance of NLR is based upon *JAK2*^{V617F} directly perturbing two immunological axes: neutrophil activation and lymphoid differentiation. Neutrophil extracellular trap (NET) formation is a normal phenomenon of innate immunity, a thrombogenic program attenuated by JAK/STAT inhibition, thereby providing a mechanistic path from clonal signaling to vascular events [5]. The *JAK2*^{V617F} pluripotent stem cells in PV preferentially augment myeloid differentiation compared to lymphopoiesis resulting in reduced *JAK2*^{V617F} lymphocytes compared to neutrophils [6, 7]. There is also evidence that *JAK2*^{V617F} impairs lymphoid differentiation, offering a genetic rationale for the lymphogenic denominator of elevated NLR in PV [8]. The NLR, therefore, may be viewed as a composite marker of both *JAK2* mutation-driven myeloid overactivity alongside compromised adaptive immunity.

JAK2^{V617F} VAF is a key determinant of risk for thrombosis and molecular response in *JAK2*^{V617F} is associated with EFS [9]. The molecular response in PV is measured in peripheral blood leukocytes, not in enucleated red cells nor bone marrow cells. Therefore, leukocytes are the same cellular compartment in which *JAK2*^{V617F} VAF is quantified. This unity of measurement and mechanism strengthens the case for bringing leukocyte metrics into formal schemas for assessing treatment response and monitoring. While historical practice and guidelines have centered on hematocrit targets to mitigate cardiovascular events, newer data support explicit incorporation of leukocyte-derived markers into risk stratification and treatment goals.

JAK2-mutant neutrophils are not "normal" effectors caught in the crossfire, but rather mutation-transformed, peripheral neoplastic derivatives of the malignant clone

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[10]. In PV and ET, the mutated PV neutrophils are the major source of prothrombotic factors including tissue factor [11, 12]. Further, PV and ET neutrophils have decreased levels of antithrombotic transcription factor KLF2, and this decrease is ameliorated by IFN but not by hydroxyurea [13]. Recent work has also shown that senescent *JAK2*^{V617F} neutrophils evade homeostatic clearance via CD24 upregulation, accumulate in tissues, promote TGF-β activation, and drive myelofibrosis; antibody blockade of CD24 restores mutant neutrophil clearance and mitigates fibrosis in mouse models [14]. It may be argued that neutrophils should be placed along the causal chain of PV complications and progression. Concurrently, NET-primed neutrophils link clonal signaling to thrombosis, reinforcing the thesis that reducing the burden of *JAK2* mutation-carrying neutrophils is both biologically and clinically meaningful.

The recent seminal work by Barbui et al. showed that ropeginterferon alfa-2b (ropeg) reduces NLR primarily by suppressing neutrophils with relative lymphocyte sparing, and that NLR decline correlates with *JAK2*^{V617F} VAF reduction and better EFS [2]. These observations corroborate randomized and prospective studies in which ropeg demonstrated superior, durable hematologic and molecular responses compared with hydroxyurea or phlebotomy-based strategies [15, 16]. Ropeg is a long-acting IFN-a-based therapy, which exerts clinical activities by activating type 1 IFN receptors. The binding of type 1 IFN receptors activates signal pathways and cause tumor cell apoptosis, cell cycle inhibition and senescence accompanied by a loss of tumorigenesis, and immune-stimulated antitumor responses [17–20]. Clinically, IFN exposure is associated with improved myelofibrosis-free and overall survival [21–23]. Together, these data align neatly: IFN selectively suppresses the *JAK2*-mutant hematopoietic clone favoring myelopoiesis including neutrophils, normalizes NLR and consequently *JAK2*^{V617F} VAF, and is associated with improved long-term outcomes. Further, only IFN therapy has been demonstrated to reactivate normal hematopoietic stem cells from dormancy as demonstrated by using X-chromosome expression-based clonality assays [24, 25]. Here, the conversion of PV clonal myelopoiesis to polyclonal takes place by demonstrating that neutrophils, platelets, and reticulocytes are converted from expressing only single same polymorphic X-chromosome allele, either maternal or paternal X-chromosome, but not both. However, after successful IFN therapy, some PV females convert to having mixture of cells, some expressing maternal while other paternal active X-chromosome, i.e. polyclonal hematopoiesis [24, 25].

There are possible practical implications with remaining questions. A relevant question is whether there is a need to further recognize the importance of *JAK2*-mutant neutrophils in PV and act on NLR routinely a readily available, prognostic marker in clinical practice. We support the notion regarding integrating NLR into regular PV monitoring. Given its demonstrated association with *JAK2*^{V617F} VAF dynamics and EFS, thresholds (e.g., ≥4–5) used in prior studies could be prospectively harmonized and validated across settings. Secondly, is there a need to normalize leukocyte-based inflammation? In patients with persistently elevated NLR and/or leukocytosis despite hematocrit control, it warrants a treatment selectively decreasing neutrophils. In this respect, ropeg is a suitable treatment option given the ability to suppress neutrophils, reduce NLR, and lower *JAK2*^{V617F} VAF in randomized trials. Furthermore, since *JAK2*^{V617F} VAF is assessed in peripheral leukocytes (mixture of clonal neutrophils and polyclonal lymphocytes [6]), it further justifies determining VAF in isolated clonal neutrophils, rather than determining VAF in polyclonal total leukocytes. The paired strategy of serial NLR and VAF could offer a viable alternative for assessing both inflammatory and clonal control in routine practice. Finally, NLR is a ratio. We suggest future analyses explicitly partition NLR dynamics into absolute-neutrophil-count- and absolute-lymphocyte-count-driven components and evaluate their independent associations with VAF and clinical outcomes. This could clarify how much prognostic power NLR derives from neutrophil suppression (clonal myeloid activity) versus lymphocyte restoration (immune competence) and may help define treat-to-target thresholds for each and improve our understanding of pathophysiology of PV.

Therefore, existing evidence indicates the notion that *JAK2*-mutated neutrophils function as mutation-transformed clonal neoplastic cells in PV and need to be integrated in the monitoring and treatment considerations of PV. NLR is accessible, inexpensive, and biologically informative; using it alongside VAF can underpin a modern strategy to capture the dynamics of both the malignant clone itself and the inflammatory sequelae.

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Declarations

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References

1. Carobbio A, Vannucchi AM, De Stefano V et al (2022) Neutrophil-to-lymphocyte ratio is a novel predictor of venous thrombosis in polycythemia Vera. Blood Cancer J 12:28
2. Barbui T, Ghirardi A, Empson V et al (2025) Neutrophil-to-Lymphocyte ratio as surrogate for JAK2V617F suppression and event-free survival in polycythemia vera. Blood Cancer J 15(1):132
3. Barbui T, Carobbio A, Ghirardi A et al (2024) Neutrophil-to-lymphocyte ratio as a prognostic indicator of mortality in Polycythemia Vera: insights from a prospective cohort analysis. Blood Cancer J 14(1):195
4. Gerds AT, Mesa R, Burke JM et al (2024) Association between elevated white blood cell counts and thrombotic events in polycythemia vera: analysis from REVEAL. Blood 143(16):1646–1655
5. Wolach O, Sellar RS, Martinod K et al (2018) Increased neutrophil extracellular trap formation promotes thrombosis in myeloproliferative neoplasms. Sci Transl Med. https://doi.org/10.1126/scitranslmed.aan8292
6. Jamieson CH, Gotlib J, Durocher JA et al (2006) The JAK2 V617F mutation occurs in hematopoietic stem cells in polycythemia vera and predisposes toward erythroid differentiation. Proc Natl Acad Sci USA 103(16):6224–6229
7. Swierczek S, Prchal JT (2020) Clonal hematopoiesis in hematological disorders: three different scenarios. Exp Hematol 83:57–65
8. Choi DC, Messali N, Uda NR et al (2024) JAK2V617F impairs lymphoid differentiation in myeloproliferative neoplasms. Leukemia 38(11):2487–2491
9. Harrison CN, Mead AJ, Panchal A et al (2023) Ruxolitinib versus best available therapy for polycythemia Vera intolerant or resistant to hydroxyurea (MAJIC-PV): a randomized, multicenter trial. J Clin Oncol 41(19):3534–3544
10. Duan M, Bose P, Hunter AM et al (2025) Emerging significance and implications of a durable complete molecular remission in the treatment of polycythemia vera. Curr Hematol Malig Rep 20(1):13
11. 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
12. Reeves BN, Kim SJ, Song J et al (2022) Tissue factor activity is increased in neutrophils from JAK2 V617F-mutated essential thrombocythemia and polycythemia vera patients. Am J Hematol 97(2):E37–E40
13. Song J, Kim SJ, Gollamudi J, Thiagarajan P, Prchal JT (2023) Downregulated KLF2 in polycythemia vera and essential thrombocythemia induces prothrombotic gene expression. Blood Adv 7(5):712–717
14. Khatib-Massalha E, Di Buduo CA, Chédeville AL et al (2025) Defective neutrophil clearance in JAK2V617F myeloproliferative neoplasms drives myelofibrosis via immune checkpoint CD24. Blood 146(6):717–731
15. Gisslinger H, Klade C, Georgiev P et al (2020) Ropeginterferon alfa-2b versus standard therapy for polycythaemia Vera (PROUD-PV and CONTINUATION-PV): a randomised, non-inferiority, phase 3 trial and its extension study. Lancet Haematol 7(3):e196–e208
16. Barbui T, Vannucchi AM, De Stefano V et al (2023) Ropeginterferon versus standard therapy for low-risk patients with polycythemia vera. N Engl J Med Evid 2(6):EVIDoa2200335
17. Qin XQ, Tao N, Dergay A et al (1998) Interferon-beta gene therapy inhibits tumor formation and causes regression of established tumors in immune-deficient mice. Proc Natl Acad Sci USA 95:14411–14416
18. Qin XQ, Runkel L, Deck C et al (1997) Interferon-beta induces S phase accumulation selectively in human transformed cells. J Interferon Cytokine Res 17:355–367
19. Kaynor C, Xin M, Wakefield J, Barsoum J, Qin XQ (2002) Direct evidence that IFN-beta functions as a tumor-suppressor protein. J Interferon Cytokine Res 22(11):1089–1098
20. Qin A (2023) An anti-cancer surveillance by the interplay between interferon-beta and retinoblastoma protein RB1. Front Oncol 13:1173467
21. Quintás-Cardama A, Kantarjian H, Manshouri T et al (2009) Pegylated interferon alfa-2a yields high rates of hematologic and molecular response in patients with advanced essential thrombocythemia and polycythemia vera. J Clin Oncol 27:5418–5424
22. Abu-Zeinah G, Krichevsky S, Cruz T et al (2021) Interferon-alpha for treating polycythemia vera yields improved myelofibrosis-free and overall survival. Leukemia 35(9):2592–2601
23. 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 37:2129–2132
24. Liu E, Jelinek J, Pastore YD, Guan Y, Prchal JF, Prchal JT (2003) Discrimination of polycythemias and thrombocytoses by novel, simple, accurate clonality assays and comparison with PRV-1 expression and BFU-E response to erythropoietin. Blood 101(8):3294–3301
25. Tashi T, Swierczek S, Kim SJ et al (2018) Pegylated interferon Alfa-2a and hydroxyurea in polycythemia Vera and essential thrombocythemia: differential cellular and molecular responses. Leukemia 32(8):1830–1833