LETTER to the EDITOR **Editorial Process:** Submission:04/13/2025 Acceptance:11/17/2025 Published:11/21/2025

Critical Appraisal of Limitations in the Study on JAK2V617F Zygosity and Disease Outcomes in MPNs

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Dear Editor

We commend the authors for their thoughtful and well-executed study, "Frequency of JAK2V617F Mutation Zygosity and Impact on Disease Outcome in MPN Patients" [1]. The work contributes valuable data on the clinical implications of JAK2V617F zygosity in myeloproliferative neoplasms (MPNs). However, several limitations should be addressed in future research to strengthen the study's clinical utility and generalizability.

One key limitation is the cross-sectional design, which limits the ability to assess long-term disease outcomes. A longitudinal approach would provide deeper insights into how zygosity influences disease progression, leukemic transformation, or fibrotic evolution over time [2]. Additionally, the small sample size, particularly in subgroups such as essential thrombocythemia (ET) and myelofibrosis (MF), weakens statistical power. This may hinder the detection of meaningful differences between homozygous and heterozygous patients within these MPN subtypes.

Another concern is the single-center recruitment, which could introduce selection bias. Patients referred to a national hematology center may have more severe disease or specific characteristics that differ from the general MPN population [3, 4]. As a result, the findings may not be broadly applicable. Multi-center studies involving a more diverse patient base would enhance external validity.

The study population was drawn exclusively from an Iraqi cohort, which may limit generalizability to other ethnic or geographic groups. Genetic and environmental differences can affect the prevalence and clinical impact of JAK2V617F mutations [5, 6]. Including patients from varied backgrounds in future studies would provide a more representative understanding.

Importantly, the study did not account for treatment regimens such as hydroxyurea, interferon, or JAK inhibitors. These therapies can significantly influence allele burden and clinical outcomes. Incorporating treatment history and response data would help clarify how therapy interacts with zygosity to affect disease course [7, 8].

Thrombotic events, a major source of morbidity and mortality in MPN patients, were also not assessed [9, 10]. Since JAK2V617F zygosity may be linked to thrombotic risk, evaluating this relationship is essential for a comprehensive clinical picture.

The exclusive use of peripheral blood samples for mutation analysis is another limitation. While convenient, peripheral blood may not fully reflect the disease's clonal complexity. Bone marrow analysis, as the primary site of disease activity, could offer richer insights into mutational burden and clonal architecture [11, 12].

In addition, inflammatory markers such as cytokines or C-reactive protein were not examined. Inflammation plays a key role in MPN pathogenesis and symptom burden. Assessing inflammatory parameters could shed light on the biological mechanisms connecting zygosity with clinical severity [13].

Finally, the study did not explore co-occurring mutations like ASXL1, TET2, or IDH1/2. These "second-hit" mutations are common in MPNs and can significantly modify the effects of JAK2V617F on disease behavior and prognosis [14, 15]. Including mutational profiling in future research would enhance risk stratification and inform personalized treatment strategies.

In conclusion, while the study offers important insights into the role of JAK2V617F zygosity in MPNs, future research should adopt a longitudinal, multi-center approach with larger, more diverse cohorts. Integrating clinical, genetic, epigenetic, and inflammatory markers will be crucial to improving the robustness and relevance of findings in real-world settings.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Meerab Sohail[1], Adeenah Irshad[2]*, Muhammad Hamza[3]

*[1]Internal Medicine, Student, FMH College of Medicine and Dentistry, Lahore, Pakistan. [2]Medicine, Student, Liaquat University of Medical and health Sciences, Jamshoro, Pakistan. [3]Internal Medicine, Student Saidu Medical College, Swat, Pakistan. *For Correspondence: irshad.adeenah@gmail.com*