

Comment on “Validation and Modeling of Flow Cytometric CD36 Coefficient of Variation (CV) Analysis in the Diagnosis of Lower-Risk Myelodysplastic Syndromes”

“Alt Risk Miyelodisplastik Sendromların Tanısında Akım Sitometrisi CD36 Varyasyon Katsayısı (CV) Analizinin Validasyonu ve Modellemesi” Üzerine Yorum

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To the Editor,

The recent article titled “Validation and Modeling of Flow Cytometric CD36 Coefficient of Variation (CV) Analysis in the Diagnosis of Lower-Risk Myelodysplastic Syndromes” [1] is interesting. This work presents strong empirical data on the function of the CD36 coefficient of variation (CV) in detecting red blood cell abnormalities and diagnosing myelodysplastic syndrome (MDS), particularly in low-risk patients. Although the mean CD36 CV value in MDS patients was higher than that of a control group, the difference was not statistically significant, suggesting the effect of the disease's biological variability, small sample size, or technical variations in measurement. However, the constant trend of elevated CD36 CV levels across patient groups suggested that this indicator has potential, especially when utilized together with other indicators rather than as a standalone diagnostic tool.

The study found that combining the CD36 CV value with the Ogata score improved diagnostic specificity from 33.3% to 80% at a cut-off value of ≥ 3 points with an area under the curve value of 0.754. This supports its efficacy in MDS evaluation, especially for low-risk patients. A multivariate approach is required since bone marrow abnormalities in this patient population are frequently not severe enough to be recognized with a single parameter. However, the decreasing sensitivity with higher cut-off values indicates a trade-off between reducing false positives and the potential of failing to diagnose patients with moderate anomalies. Physicians must weigh this tradeoff carefully while considering the particular clinical situation.

The study's main limitations included its retrospective nature and small sample size, which may have impaired the statistical power to detect variations in CD36 CV levels, particularly in low-risk MDS patients. Furthermore, applying a cut-off based on a single center's data may have limited the applicability to various

other clinical contexts because flow cytometry parameters vary depending on the device, parameter settings, and gating approaches. These variables could contribute to the statistical variability observed in the study.

Overall, this study showed that the CD36 CV can greatly improve the performance of current scoring systems, including the Ogata score, even though it is not a reliable diagnostic tool on its own. This further reflects a recent trend in the development of markers that give priority to anomalies in the red blood cell lineage. Comprehensive studies with larger sample sizes should form the basis of future research initiatives. The objectives of future multicenter studies should be to generate a uniform standardized CD36 CV score, incorporate additional erythroid dysplasia markers into multivariate models, and employ machine learning approaches to produce more precise prediction tools. The findings of the study by Akar et al. [1] provide a crucial foundation for future advancements in the use of flow cytometry in the diagnosis of low-risk and early-stage MDS.

Keywords: Flow cytometry, CD36, Coefficient of variation, Myelodysplastic syndromes

Anahtar Sözcükler: Akım sitometrisi, CD36, Varyasyon katsayısı, Miyelodisplastik sendromlar

Ethics

Informed Consent: Not applicable.

Footnotes

Authorship Contributions

Concept: H.D., V.W.; Design: H.D., V.W.; Data Collection and Processing: H.D., V.W.; Analysis or Interpretation: H.D., V.W.; Literature Search: H.D., V.W.; Writing: H.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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Reference

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Reply from the Authors:

We thank Daungsupawong and Wiwanitkit for their interest in our study and their thoughtful interpretation of our results. Although their commentary does not contain direct criticism, we would like to clarify some of the points mentioned.

As stated in our original study, the most important limitation of the work was the small sample size [1]. Our efforts to homogeneously include flow cytometric data from a retrospective cohort resulted in a small sample, which led to the statistical analysis being insufficient in some areas. This limitation is acknowledged both in the original manuscript and in this response.

Since myelodysplastic syndrome diagnosis is a clinical diagnosis of exclusion supported by laboratory findings, flow cytometric data are not yet a gold-standard diagnostic tool but rather a supportive element. For this reason, and due to the heterogeneity in both the degree and nature of dysplasia among patients, including more flow cytometric parameters in the diagnostic process decreases the specificity. This challenge is driving new research in flow cytometric MDS diagnosis. The same heterogeneity limits the diagnostic power of a single parameter; just as CD36 alone did not produce meaningful results in our study, it needs to be used in combination with other immunophenotypic features. Evaluating the model strength of various combinations was the main objective of our study.

Unlike straightforward positive/negative immunophenotype results, analyses based on variables such as the coefficient of variation (CV) or median fluorescence intensity using flow

cytometric data are significantly affected by interlaboratory variations including the device and its pre-analytical settings, fluorochrome selection, panel design, and gating strategy. Establishing local standards (e.g., cut-off values) according to guiding standards is a solution to this problem. For this reason, in a strong multicenter study on flow cytometric erythroid immunophenotyping in MDS diagnosis that serves as a reference for the International/European LeukemiaNet Working Group for Flow Cytometry in Myelodysplastic Syndromes guidelines, Westers et al. [2] recommended that each center determine local CD36 CV cut-offs based on their own non-MDS data and published an algorithm including a standardized calculation approach for this purpose. In our study, we determined cut-offs from a local cohort both to validate previous studies and to incorporate the system described by Westers et al. [2] into our own laboratory.

As Daungsupawong and Wiwanitkit state here, more comprehensive studies with broader parameters and multicenter collaborations are needed in this promising area. Strengthening the power of manual analyses like those in our study with machine learning and implementing broader models with other clinical and laboratory findings can be considered. Efforts are ongoing both within our research group and globally in this regard.

Sincerely,

Emre Akar, Şüheda Çakmak, Mehmet Baysal, Seval Akpınar, Burhan Turgut

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