

Is RBC discrimination index suitable for differentiating between α - and β -thalassemias?

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Hemoglobinopathies impose a significant burden on global healthcare. Approximately 5–7% of the global population carries a potentially pathological hemoglobin gene. This mainly includes the structural hemoglobin variants and different forms of thalassemias. Among the thalassemias, β -thalassemia is very common and is mainly seen in Greece, Cyprus, Italy, the Middle East, and the Indian subcontinent.^[1] Detection of β -thalassemia traits (BTTs) or carriers is one of the important steps in the control program for thalassemia. A battery of tests like peripheral blood smear examination, RBC indices, and estimation of HbA₂ level are used to identify a carrier. It is known that RBCs from a β -thalassemia carrier are microcytic and hypochromic. Iron deficiency anemia (IDA) is the most common nutrient disorder in the world.^[2] This entity also shows microcytic hypochromic RBCs.

RBC indices are part of a complete blood count and are used to diagnose the cause of anemia. The mechanism by which anemia occurs alters the RBC indices in a predictable manner. Mean corpuscular volume (MCV) is considered as the most informative parameter and anemias can be categorized as microcytic (MCV <78 fl), normocytic (MCV 80–90 fl), and macrocytic (MCV >100 fl). Both β -thalassemia carriers and IDA cause microcytic

anemia. Therefore, several attempts have been made to differentiate between these two conditions by using RBC indices. In the last four decades, several formulae have been designed for this purpose.^[3–6] However, none of the formulae has been found to be 100% sensitive or specific for differentiating these two entities. Recently, Niazi *et al.* (2010)^[7] analyzed 312 patients (213 BTT and 89 non-BTT) from Pakistan by calculating seven discrimination indices and found that none of them showed 100% sensitivity and specificity. The percentage of correctly diagnosed cases was the highest for Red Cell Distribution Width Index (RDWI) (84.19%) followed by Mentzer Index (86.85%). It is interesting to note that Jiminez (1993)^[8] conducted similar analysis and found that the sensitivity and specificity were only 86.9 and 80.1%, respectively; however, when serum iron concentration was included along with RBC indices to differentiate between BTT and IDA, the sensitivity and specificity rose to 94.2 and 91.6%, respectively, indicating the necessity of some additional test along with RBC indices for differentiation between BTT and IDA.

In the α -thalassemias, the most common mutations are of the deletional type. It has been observed that these mutations also decrease the size of RBCs and alter other RBC indices like in β -thalassemia.^[9,10] However, effective screening tests have not been developed so far and DNA analyses remain the only option for accurate diagnosis. Nonetheless, attempts have been made to evaluate various RBC indices for screening α -thalassemia. Sirichrotiyakul *et al.* (2009)^[11] evaluated the use of the osmotic fragility test and MCV to screen for α -thal 1 and / or β -thal in pregnant women from Thailand and found more than 90% sensitivity for both

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the tests. Pranapanus *et al.* (2009)^[12] considered Hb content and not the size of RBCs for screening α -thal (SEA type) and BTT in pregnant ladies from Thailand. They considered mean corpuscular hemoglobin (MCH) as the best tool for screening and considered MCH <26.5 pg as the best cut-off level for predicating thalassemia carriers. This MCH level gave a sensitivity of 95.2%. Tayapiwatana *et al.* (2009)^[13] developed a novel strategy for screening of α -Thal 1 carriers in Thailand. A sandwich type immunochromatographic strip was developed using monoclonal anti-Bart's antibody. This strip, along with RBC indices, was found to be suitable for screening mass populations for α -thal 1.

In the present issue, Mehdi and Al Dahmash (2011)^[14] have tried to differentiate between α - and β -thalassemia carriers from Saudi Arabia using RBC indices. The prevalence of α + thalassemia allele in Peninsular Arabs varies between 0.07 and 0.58 (El Hazmi 1982).^[15] The prevalence of β -thalassemia is also high and extremely heterogenous at the molecular level.^[16] In both α - and β -thalassemias, varying degree of microcytosis has been observed. In a population like the one from Saudi Arabia, where both α - and β -thalassemias are common along with IDA, there is a possibility that individuals with a combination of any two of the defects are likely to be present. Since the cut-off values for various RBC indices are overlapping in these conditions, the indices alone may not be conclusive to differentiate these entities. In the present study, carriers of α gene deletions had mild microcytosis with or without anemia. The co-existence of α gene deletions generally modifies the phenotype of β -thalassemia patients. In the present study, several cases of BTT as well as of α -thal deletions had normal MCV and MCH values. Thus, the authors concluded that RBC indices only cannot be used to differentiate between α - and β -thalassemias. It could be argued that in this population, using some simple tests like serum iron concentration (Jiminez 1993)^[8] or an immunochromatographic strip for screening for α -thalassemia (Tayapiwatana *et al.* 2009)^[13] would be helpful along with RBC indices to differentiate between α - and β -thalassemias. If such a strategy is developed successfully, it would be helpful

in the laboratories where hemoglobin electrophoresis is not available.

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