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Letter to the Editor

Assessment of the Matos & Carvalho index for distinguishing thalassemia from iron deficiency anemia

Dear Editor,

In a recent issue of this journal, Matos et al. proposed a new index for discriminating between iron deficiency anemia (IDA) and the thalassemia trait.[1] We read their paper with great interest, since we have performed similar research in this field.[2] Recently we completed a study in which we compared 25 discriminant formulas incorporating only basic red blood cell (RBC) parameters using a large database of patients with mild microcytic anemia, who either had a diagnosis of IDA or were thalassemia carriers.[3] This database now gives us the opportunity to investigate the diagnostic performance of the Matos & Carvalho (M&C) index in a much larger patient cohort than the authors used for their development and validation,[1] and we present our findings in this communication.

Our database comprises 2664 patients with microcytic anemia, defined as hemoglobin <13 g/dL and mean corpuscular volume (MCV) <80 fL, irrespective of gender. It was built over a period of nine years, during which time the Beckman Coulter LH780 was the main hematology analyzer in use; other hematology analyzers were operated for shorter periods. Standard biochemical and hematological methods were used to make the diagnosis; the diagnosis of α-thalassemia was based on molecular techniques. Of our patients, 1196 had "pure" thalassemia (319 α-thalassemia and 877 β-thalassemia), 1259 had simple IDA, 117 had thalassemia with concomitant IDA, 33 had thalassemia with concurrent anemia of chronic disease, 23 had complex thalassemia and 36 had other diseases associated with microcytic anemia.

When applying the M&C formula to our database in the receiver operating characteristic (ROC) analysis, we found an area under the curve (AUC) of 0.892 (95% confidence interval: 0.879–0.904); as Figure 1 demonstrates this AUC is significantly (p-value < 0.0001) lower than the three best performing formulas in our study that all had AUCs around 0.95.[3] At the optimal cut-off of 23.6, the M&C index resulted in 0.854 sensitivity, 0.795 specificity and a Youden index of 0.649. If we had included the M&C index in our study, then it would have ranked 18 out of the 26 formulas investigated. This is in clear contrast with the findings of Matos et al., who reported excellent diagnostic accuracy of their new index. However, it is not at all unusual for authors of new discriminant indices to overestimate the performance of their invention, as evidenced by independent validation studies.[3]

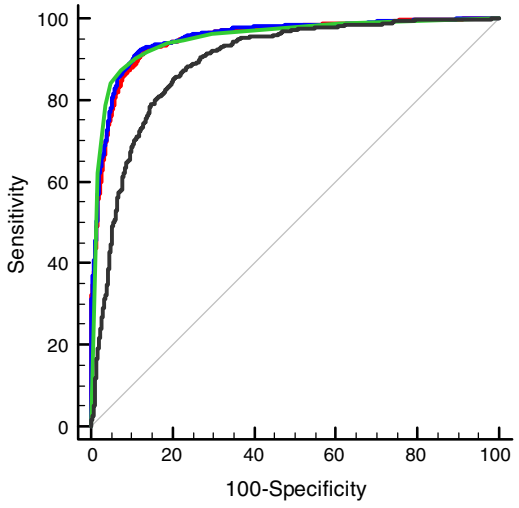

Figure 1 – Receiver operating characteristic (ROC) analysis of the Matos & Carvalho (M&C) index (black) in comparison with the Janel (green), Green & King (red) and Jayabose (blue) formulas for differentiating iron deficiency anemia from the thalassemia trait.

When considering potential reasons for this disagreement, several factors may play a role. Firstly, Matos et al. derived their index from a population of 106 patients, of whom only 23 had the thalassemia trait. Also their validation group had a small minority of thalassemia carriers, only 16%. In our study group, the proportion of "pure" thalassemia amounted to 45%. Both α- and β-thalassemia have very heterogeneous

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genetic backgrounds, so this number of thalassemia patients in their study may have been too low to properly characterize the various carrier subtypes; alternatively, the disagreement may be due to local characteristics of the population in the area investigated. Secondly, Matos et al. excluded patients with concomitant IDA and the thalassemia trait; it has been repeatedly demonstrated that this condition causes many discriminant formulas to give an incorrect classification and by excluding this group, they may have introduced a bias in favor of their new index. If we exclude such patients from our analysis, the performance of all discriminant formulas would increase, but this would no longer realistically reflect clinical practice, as approximately 5% of patients with microcytic anemia suffer from IDA associated with the thalassemia trait. Thirdly, the M&C index includes the mean corpuscular hemoglobin concentration (MCHC), a calculated parameter that is known to have relatively weak correlation between different hematology analyzers. Although the type of hematology analyzer was not found to have much impact on the performance of discriminant functions,[2] a possible role cannot be excluded. In this context, it is of interest that the MCHC alone has a very poor performance for distinguishing IDA and thalassemia.[2]

In conclusion, we are unable to confirm the finding by Matos et al. that their new M&C index has excellent performance for discriminating iron deficiency anemia from the thalassemia trait. As a matter of fact, we do not recommend laboratories use any newly published index without additional validation in their own patient population.

Conflicts of interest

Johannes Hoffmann is a scientific employee of Abbott Diagnostics; Eloísa Urrechaga has no conflicts of interest to declare.

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