Critical Considerations on Interpreting N-Terminal Pro-Brain Natriuretic Peptide levels in Kawasaki Disease

We read with interest the study by Banerjee et al on N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) levels in Kawasaki Disease (KD) [1]. The authors reported that the number of KD patients whose NT-proBNP was elevated (n = 28) were significantly higher compared to controls (70% vs 32.5%; P < 0.001). Also, children with incomplete presentations of KD had higher NT-proBNP levels than controls (84% vs 4%; P < 0.001). It is appropriately mentioned that difficulty in identifying incomplete and atypical presentations of KD could delay the diagnosis and increase the risk of coronary involvement [2]. Therefore, in this study, it would be interesting to know the proportion of incomplete KD among the cases and the number of incomplete KD cases that had higher NT-proBNP levels. The apparently high proportion of incomplete KD patients with elevated NT-proBNP (84%) compared to complete KD (70%) and controls (4%) in this study indicates that elevated NT-proBNP levels may have played a role in the diagnosis of incomplete KD. This could have potentially introduced a selection bias.

In current clinical practice, it is compelling to use age-specific centiles for NT-proBNP in contrast to a fixed cut off value (225 pg/mL) as considered in the study [3,4]. NT-proBNP levels are known to decrease with age, from 400 pg/mL at 3 months to 138 pg/mL (female) and 65 pg/mL (males) by puberty, and even within the 1-2 years age-group, the cut offs vary between 316 to 675 pg/mL [4]. Using a single value instead of age- and gender-stratified cut-offs could be potentially misleading.

Interpreting NT-proBNP thresholds also requires careful consideration of the specific patient population and clinical context in which the test is being used. A recent meta-analysis of pooled data from 12 studies (2173 cases and 1909 controls) indicated that NT-proBNP has a moderate diagnostic accuracy for KD with the pooled sensitivity and specificity of 0.80 (95% CI: 0.72-0.86) and 0.81 (95% CI: 0.73-0.88), respectively [5]. Prevalence-adjusted NT-proBNP thresholds potentially improve the test’s performance. In areas where KD is not widespread (prevalence < 10%), a negative NT-proBNP test provides strong evidence against KD [5].

The clinicians need to consider the individual patient’s risk factors and clinical judgement in addition to prevalence of KD in their setting when assessing the likelihood of KD while interpreting NT-proBNP values. Especially in cases of incomplete presentations of KD; understanding the patient’s pre-test probability can be crucial for accurate diagnosis. For practitioners in low-prevalence settings, dependence on NT-proBNP as a diagnostic tool may lead to over diagnosis and unnecessary interventions.

REFERENCES

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AUTHORS’ REPLY
We thank the authors for carefully reading our article on NT-proBNP levels in Kawasaki Disease (KD) and the accompanying critical appraisal. Their query is mainly centered around “It was also shown that even patients with incomplete KD had higher NT-proBNP levels than febrile control group (84% vs 4%; P < 0.001).” However, this was not mentioned in the results of our study and was mentioned in the paragraph in the discussion section where we discussed our study findings in comparison to previous published articles. This particular finding was from the study published by Rodriguez-Gonzalez et al in Emergencias in 2019 [1]. We faultily missed out adding the reference. Thus, the presumption that elevated levels in incomplete KD patients resulted in selection bias is not true.

The authors have questioned our fixed NT-pro BNP cut off value and have rightfully advised for usage of age and gender specific cut-offs. Since we were conducting a comparative study of levels in a heterogeneous group (KD patients vs other febrile controls) we thought it to be more convenient to have a single cut-off. Moreover, our study