Dr. Abdirahman and colleagues have investigated the relationship among widespread endothelial activation (soluble angiotensin-2 (sAng2) levels), Plasmodium falciparum-infected erythrocyte (IE) phenotype (expression of Group A and/or rosetting PfEMP1), and clinical presentation (non-severe, severe (subdivided into impaired consciousness (IC), cerebral malaria (CM), respiratory distress (RD), and severe malarial anemia SMA)) in Kenyan children.

The objective was to obtain evidence of a causal link between IE phenotype/clinical presentation and widespread endothelial activation.

It appears that all data analyzed, except for ELISA data on levels of sAng2 and P. falciparum histidine-rich protein-2 (PfHRP2), were obtained from previous studies (mainly the two papers by Warimwe et al., cited as refs. 7, 8).

The authors report a number of associations between sAng2 on the one hand and IC, RD, Group A, rosetting on the other, and use complex statistical analysis to propose various causal relationships. However, the overall conclusion, based on the balanced Discussion of the data presented and the literature is that it remains unresolved whether endothelial activation is mainly a consequence of IE sequestration or the result of circulating proinflammatory factors (e.g., toxins, microparticles), and that more studies are needed.

In my opinion, the study casts interesting new light on the complex pathogenesis of severe P. falciparum malaria.

MINOR ESSENTIAL REVISIONS

General (1): Previous work by the authors and others has shown that age is a major predictor of malaria susceptibility and severity, antibody levels, parasitemia etc. There is no mention of the effect of age in the present manuscript, although the age of the patients studied ranged from a few months to more than 12 years (according to the Warimwe et al. paper from 2009). Please explain why age was not considered (if it wasn’t) or how (if it was).

General (2): It would be helpful to the reader, if the rather technical, statistics-based conclusions were complemented with a more biological conclusion/interpretation throughout the manuscript. As an example, what biological/pathogenic pathways do the authors suggest might be operating when
they write “distinct pathways may link group-A like var expression and widespread endothelial activation to IC” (L. 230-2)?

General (3): The authors ought to reconsider their choice of literature references, which at places appears biased towards their own work and ignoring original contributions by others.

L. 115: Correct spelling mistake (“clonies”).

L. 151-4: “… where IC, RD, or cerebral is the outcome”. Change “cerebral” to “cerebral malaria”. Change these sentences (and other (partially) present-tense sentences scattered through the MS, e.g., L. 190-3) to past tense.

L. 174-85 and Fig. 1A: Suggest including medians and their 95% confidence intervals to text and/or Fig. 1A (like in Fig. 1B). This would make it easier for the reader to evaluate the biological significance of the statistically significant difference, considering the very substantial overlap of values from severe and non-severe patients.

L. 174-85 vs. L. 198-213: A conclusion of both these sections is that sAng2 is associated with IC (L. 183-4 and

L. 181: Change “multivariable” to “multivariate”.

L. 187: “Given the potential link…”. Please explain where and how this link is “given”. Presently it appears as a (quite plausible) postulate only.

L. 208-9, respectively). Please explain why both sets of statistical analysis are pertinent (i.e, why they are both needed).

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.