Reviewer’s report

Title: C-reactive protein as a potential biomarker for disease progression in dengue: A multicountry observational study

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Reviewer: Junxiong Pang

Reviewer's report:

This study presents an important research for dengue triage for early dengue management to reduce dengue severity. The authors aimed to evaluate if dengue patients with higher CRP levels in the early febrile phase are at higher risk of developing severe disease. In addition, they aimed to evaluate if dengue patients have higher CRP levels than patients with other viral febrile illnesses. However, it was noted these hypotheses are not novel and had been tested in a number of studies, albeit with small sample sizes. Moreover, there are areas that may be important to consider to strengthen this important analysis, which are listed below.

Major comments:

1. Method (Study design) - "Hospital admission and individual case management were determined according to clinical need, with all interventions documented in the case report forms."- It may be important to list down key interventions (such as blood, platelet transfusion) that were part of patients' case management to assess if there is any potential intervention that may be a confounding factor, affecting the CRP level too.

2. Method (Study design) - "Subsequently each participant was assigned an overall severity grading using all available information" Would there be any potential classification bias if the severity grading is not based on a standardized framework or variables?

3. Method (Study population) - "This cohort included 38 severe and 248 intermediate severity cases (combined primary outcome of 286 cases). The 286 cases were compared to 847 uncomplicated dengue patients as controls (1:3), based on similar geographic and demographics and day of illness (DOI) making a total sample size of 1133 dengue cases" How were the 1133 samples among 2694 laboratory confirmed dengue selected for CRP testing? Are the demographic of those selected for CRP testing significantly different from those not tested?

4. Method (Statistical analysis) - "The model comparing CRP levels between dengue and OFI groups was adjusted for age and day of illness (DOI) at enrolment. " It is not very clear on the justifications that the authors had to adjust for age and DOI since they were "matched" and Table 1 did not showed significant differences in median for age and proportion for DOI between OFI and dengue?
5. Method (Statistical analysis) - "Other models for association between CRP levels and dengue severity were adjusted for age, DOI at enrolment, plasma viremia levels at enrolment, and immune status." It is not very clear on the justifications that the authors had to adjust for age and DOI since Table 1 did not showed significant differences in median for age and proportion for DOI between dengue severity? Other potential confounding factors such as primary/secondary dengue status, bacteria co-infection, use of antibiotics and length of fever days, and any other comorbidities should also be adjusted as these factors may also be associated with CRP levels.

6. Results (Table 1) - Since this study involved recruitment from a number of sites, it would be prudent to assess if there is an over-representation from any sites to aid in interpretation and conclusion.

7. Results (Table 1) - As it is known than CRP is associated with comorbidities and clinical interventions during the DOI 1-3, it would be prudent to account the proportion and potential confounding effect of these factors on CRP level.

8. Results (Table 1) - Since the aim is to assess the usefulness of CRP at early febrile phase to predict the dengue severity, it would be critical to assess the median days of illness (DOI) when the respective dengue severity outcomes were observed/ diagnosed (intermediate, severe) in order to strengthen the generalisability of the use of CRP.

9. Results (Table 3) - Association testing can also be strengthened by stratifying the median CRP level at DOI 1, DOI 2 and DOI 3 at enrolment, respectively, instead of, using just median CRP at enrolment (taking into account DOI 1-3) and adjusting for DOI. The performance of CRP may be significantly different in just 1 day as also shown in Figure 2 and this can aid in better understanding and interpretation of its potential performance in one of these DOI when presented by the patients. This is also in line with criteria of "consistency" in evaluating a risk factor based on Bradford's Hill criteria.

10. Results- Since there is an interest to show potential triage application, it may be useful to show the prognostic performance of CRP as well as in addition to other clinical and/ or laboratory features using AUC, sensitivity and specificity, goodness-of-fit and likelihood-ratio test. Association testing may not be adequate to show CRP's predictive potential accurately.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.
Yes

Does the work include the necessary controls?
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