Reviewer’s report

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

Version: 0 Date: 24 Sep 2019

Reviewer: Carol Blair

Reviewer's report:

Manuscript describes a nested case control study using clinical data and samples collected from patients presenting with dengue-like illness in a multi-country study to investigate the value of elevation in serum levels of the inflammation marker C-reactive protein (CRP) early in dengue infection to predict disease outcome. The study involved large sample numbers, with patients selected representing 286 cases with severe/intermediate dengue compared to 846 cases of uncomplicated dengue and 400 cases of other febrile illnesses based on defined criteria. The patients came from 5 study sites in Southeast Asia and El Salvador. The study was based on the hypotheses that 1) Dengue patients with higher CRP levels in days 1 to 3 of the early febrile phase are at higher risk of developing severe disease, and 2) Dengue patients have higher CRP levels than patients with other viral febrile illnesses. The study found that higher CRP levels one days 1 to 3 of fever were associated with a higher risk of severe/intermediate outcome and concluded that higher CRP levels in first 3 days of illness could be a useful biomarker for early dengue risk prediction. Differences in early CRP levels were also detected between dengue patients and those with other febrile viral or bacterial illnesses.

This study aimed to harmonize somewhat divergent conclusions from previous, more limited studies. Patient samples that had been collected previously by the IDAMS consortium allowed for a well-defined and thorough study. The first serum samples had been collected early, with subsequent samples collected throughout illness and precisely analyzed for this study. The large sample size from geographically and demographically diverse populations, the variety of clinical, serological, and biochemical measurements, and the thorough statistical analysis of the data give confidence that the conclusions provide some level of assurance that a valuable biomarker for risk prediction has been identified. In addition, this study has provided an accessible POC test, since CRP assay kits are inexpensive and easily obtainable. Results may also be added to the existing data-base for differentiating dengue from other febrile illnesses. The authors also acknowledge the limitations of their study conclusions.

The study is well-written and easy to follow. This reviewer has only a few questions and corrections for the authors.

p. 8, section on "Association of CRP level and clinical outcomes among dengue patients": In Table 2, above, data for intermediate and severe dengue patients was separated into 2 columns. In this section, and in Table 3, data for intermediate and severe dengue were combined, and this was not clarified at the outset.

p. 2, line 59: Change "differentiate" to 'differentiating'

p. 4, line 28: A reference is given as "Thomas 2016" rather than a number. There is no corresponding reference in the list at the end.
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?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
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Yes

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