Reviewer's report

Title: The correlation between the presence of viremia and clinical severity in patients with enterovirus 71 infection: a multi-center cohort study

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Reviewer: Kulkanya Chokephaibulkit

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This study is looking for the relationship of viremia of EV71 and disease severity. The results may lead to an better understanding of the pathogenesis. The results suggested that presence and magnitude of viremia are not correlated with disease severity. But for those who had viremia detected after day 4 of illness had a higher proportion of severe disease.

There are some major issues need to clarify.

1. The study design for single sample collection makes it unable to firmly conclude the viremia with the severity. The disease severity and viremia are both dynamic. As there are some uncomplicated patients who were not hospitalized, how can the author be sure that the patients who were not severe at the time of blood drawn did not progress to a more severe disease in a few days later with the higher viral load. Could it be possible that the patients visited other health care institutions later when the disease become more severe?

2. The method was unclear whether the quantitative PCR was performed real time for was done in batch of stored samples. If the samples were stored, the duration of storage need to be clarify and discuss whether it could reduced the detection of viremia or reduce the viral load detected.

3. It would be helpful to understand the nature of viremia if the author can generate the figure or table to show the proportion of detectable viremia by the day of illness, according to the day that the samples were collected. For example, the viral load on day 1-2 may be found in the higher proportion or higher peak than day 3. How many samples were available by each day of illness.

4. As the viral load in a single time point cannot be determined whether it is the peak, the correlation of the viral load and severity should be compared in the very same day of illness.

5. It should be clarified that the severity grading was at the time of blood collection or at the hospital discharge.

6. The author found a higher proportion of severe diseases in the patients who had viral load detected after day 4 of illness. On the other hand, it is important to understand the reasons for more severe patients to show up late, and that was why the samples was collected in the later days. Only if author can get the serial samples of patients in various severity before the conclusion that prolonged
viremia correlate with the severity can be drawn. The conclusion that "viremia persistent for four days or after the onset of disease correlate with more severe disease" may be misleading.

6. Although the study seems to be the very first report of viremia and severity in human, there were studies in animal. The one published by Ying Zhang et al (2011) in monkey suggested that the peak viremia correlate with route of inoculation and the clinical illness. Please add this in the discussion.

**Level of interest:** An article of limited interest

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.