Author's response to reviews

Title: Extensive haemorrhagic necrosis of liver is an unpredictable fatal complication in dengue infection: a postmortem study

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Author's response to reviews: see over
Thank you very much for the reviewer comments and the prompt review of our article. We have made the necessary changes according to the reviewer comments and following are point-by-point description of the changes made. Hope this would be satisfactory.

Reviewer
1: Kumudu Karunaratne
Reviewer's report:
Minor Essential Revisions

Methods: 2nd para, 5th line ‘into’ should be one word
- correction made as ‘into’

Results:
1st para – penultimate line – indicates that there are four patients with evidence of plasma leakage but table 1 indicates only 3 patients, having a blank cell for patient 2. Preferable to fill that.
- Patient 2 had right side pleural effusion. This has been filled in table 1

Laboratory investigations:
1st para says that table 2 depicts laboratory investigations. Dengue NS1 Ag detection and serology had been used for confirmation of the diagnosis but results are not included in table 2. It would be preferable to include these results in the table for laboratory confirmation of the diagnosis especially as patients 2 and 3 have negative PCR results for dengue and confirmation of diagnosis in not evident.
- This data has now been entered into table 2.
Table 4:
4th row columns 2 and 3- mesentery spelt erroneously as mesentry.
- correction done as ‘mesentery’

7th row 4th column - spelling correction petichiae
- correction made as petichiae in 7th row 3rd and 4th columns

Reviewer 2: dominicus husada- Reviewer's report:

2. MINOR ESSENTIAL REVISIONS:

2a. Results:
Clinical presentation, 2nd paragraph: the sentence “all five patients….” (5). I think the number of the reference should be (7) instead of (5).
- reference changed to [7]

2b. Results: Any data about other infections in the patients, especially hepatotropic viruses? What about other predisposing factors (beside DM and hypertension)? This is a crucial issue considering that most patients died on day 4 to 6 with extensive necrosis of the liver
- This picture of fever with severe thrombocytopenia with flushing is very typical among Dengue fever patients in Sri Lanka and also the NS1 antigen test was positive among these patients on admission. As the diagnosis was very obvious due to the above reasons as well as due to financial constraints as Sri lankan hospitals do not have the facilities to perform routine virological studies, these other hepatotropic viruses were not analyzed.

2c. Results: Was diabetes of the patients under control or well managed?
- Diabetes was well controlled in these patients. Also they were converted to soluble insulin on admission due to critical nature of the patient. This information has been added to the manuscript under results, 1st para – 4th line.

2d. Results: Was the patient referred from another hospital or health center?
What treatment given before arrived at THP? The author need to explain more about this treatment issue since many problems raised from improper fluid management.
Two patients were transferred from a regional primary care hospital, where as the other three patients directly admitted to THP. The two patients who were transferred were send due to persisting shock with fluid leak despite fluid resuscitation. This has been inserted into Results- 1st Para- 2nd to 4th line.

2e. Table I: Any data of BMI of the patients? I consider this is better than “appearance”
- Unfortunately the patients were too ill to measure their height and calculate BMI.
**2f. Discussion : What is the distribution of dengue virus serotypes in Sri Lanka? Is Den-1 the most encountered serotype? Or is it only found on the deceased patients?**
- The four DENV serotypes (1, 2, 3, and 4) have been co-circulating in Sri Lanka for more than 30 years with one of the largest dengue epidemics occurring in 2009 due to DEN-1. This information is inserted into the Discussion 5th para- 1st line with a new reference attached as number 22. Previous reference number 22 has been removed.

**2g. Discussion : Any known data on liver histopathology of the survivors? Maybe the necrosis process also found in various stages of the disease**
- As dengue haemorrhagic fever has thrombocytopenia and a very high risk of bleeding, liver histology is generally not done in these patients. Therefore we do not have information on liver histopathology of the survivors.

**2h. Discussion : The author mentioned little information about treatment. It is stated that they followed the Sri Lanka guidelines. I guess Sri Lanka guidelines follow the WHO guidelines. Am I right?**
- Yes. That is correct. Sri Lankan guidelines follow the WHO guidelines the last being the 2011 WHO guideline.

**2i. Discussion : I suggest the author to mention several other limitations of the study. For example: some missing data of the patients**
- This limitation is now mentioned in the Discussion – 1st para- last line.

**2j. References : Is the data about the reference number 30 complete?**
- Reference 30 has been corrected in the revised manuscript.

**DISCRETIONARY REVISIONS :**

**3a. Reference number 1 is 1997 WHO Guidelines. There are 2 more recent guidelines at this moment (2009 and 2011). I believe the authors know about it.**
- Yes. The reference has been changed with reference to the WHO 2011 guideline.

**3b. Table I : I also suggest the IgM and NS1 data mentioned in the table**
- This data has now been entered into table 2. (as suggested by reviewer 1.

Thank you.
Yours trustfully,
Dr.R.A.Abeysekera (corresponding author)