

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

|                            |  |
|----------------------------|--|
| <b>TITLE (PROVISIONAL)</b> | Determinants of Mortality and Prolonged Hospital stay among Dengue patients attending Tertiary Care Hospital: A Cross-Sectional Retrospective Analysis |
| <b>AUTHORS</b>             | Mallhi, Tauqeer; khan, Amer hayat; Sarriff, Azmi; Adnan, Azreen; Khan, Yusra   |

### VERSION 1 - REVIEW

|                        |  |
|------------------------|--|
| <b>REVIEWER</b>        | Pagakrong Lumbiganon<br>Department of Pediatrics, Faculty of Medicine,<br>Khon Kaen University,<br>Khon Kaen, Thailand |
| <b>REVIEW RETURNED</b> | 21-Mar-2017  |

|                         |  |
|-------------------------|--|
| <b>GENERAL COMMENTS</b> | <p>This an interesting paper describing prolonged hospital stay and factors associated with mortality in dengue patients. I am not quite clear about the classification of DF and DHF and have few points that would like to address:</p> <p>Concerning deaths in 3 DF cases without co-morbidity, this is a bit unusual,</p> <p>1 in TABLE3 hematocrit &gt; 20% , is this means Hct rising &gt;20% from the baseline?</p> <p>If yes, it means that there were 5 out of 8 cases in fatal group with Hct.20% but it was stated that only 2/8 had DHF. Rising Hct&gt;20% is 1 of the clinical criteria of DHF.</p> <p>2 In table 4, 4 cases of fatal group had pleural effusion, which is also the clinical criteria of DHF. Six cases had shortness of breath which is unusual in DF.</p> <p>3. MODS is very unlikely to occur in DF.</p> <p>Few minor comments:<br/>The institution of the 4th author Adnan in the title page and in page 1/40 are not the same.<br/>Keywords in these 2 pages are also different.</p> <p>Thank you very much for inviting me to review this manuscript.</p> |
|-------------------------|--|

|                        |   |
|------------------------|---|
| <b>REVIEWER</b>        | Dr. Kandati Jithendra<br>Narayana Medical college<br>Chinthareddypalem, Nellore<br>Andhra pradesh<br>India. |
| <b>REVIEW RETURNED</b> | 28-Mar-2017   |

|                         |                                |
|-------------------------|--------------------------------|
| <b>GENERAL COMMENTS</b> | Good work done by the authors. |
|-------------------------|--------------------------------|

|                        |   |
|------------------------|---|
| <b>REVIEWER</b>        | Dr. Erum Khan<br>Aga Khan University, Karachi, Pakistan |
| <b>REVIEW RETURNED</b> | 03-May-2017   |

|                         |   |
|-------------------------|---|
| <b>GENERAL COMMENTS</b> | a well written report, addresses the critical question of what factors that determine the severity of patients with dengue infection especially in an outbreak situation. |
|-------------------------|---|

### VERSION 1 – AUTHOR RESPONSE

#### REVIEWER-1

Reviewer Name: Pagakrong Lumbiganon

Institution and Country: Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

Comment-1: This an interesting paper describing prolonged hospital stay and factors associated with mortality in dengue patients. I am not quite clear about the classification of DF and DHF and have few points that would like to address:

Response-1: Respected reviewer, first of all thank you so much for your time and efforts endeavored by you to review this manuscript. We are very thankful for appreciating our work. Indeed, dengue is a growing burden to the health care system, especially in tropical countries with regular epidemics of disease. Early identification of factors associated with prolonged hospitalization and mortality will lead to prioritized management of high risk patients that could be translated into reduced morbidity, mortality and hospital stay.

Comment-2: Concerning deaths in 3 DF cases without co-morbidity, this is a bit unusual

Response-2: Respected reviewer, we agree that mortality rate in DF without baseline comorbidities is extremely rare but fatal cases do occur in such instances due to several confounding factors. For example, death in DF without comorbidities has been reported (Reference 1, given below) but other factor i.e. subsequent staphylococcal infection was considered as a cause of death in DF. Similarly, in our study, death of three patients with DF in the absence of comorbidities is attributed to several other factors as described in Table 5. As we can see that these three patients were admitted late to the hospital (on day 6, 8, 5) and this delayed hospitalization might have caused abrupt deterioration in clinical condition leading to death. We have discussed all these possibilities in discussion section of the manuscript. We can also see that these three patients had severe renal failure that was also a documented cause of death among them. Furthermore, two patients were having acute respiratory distress syndrome and respiratory failure that were also among causes of death. Moreover, MODS among these three cases might be another possible cause of death (reasons of MODs in DF in given in answer of question 3). All these factors might be linked to the mortality in these three case and these factors have previously documented in the literature. It has been described that dengue exhibits unpredictable clinical progression and outcomes (Reference 2, give below) and we believe that death in dengue fever without any comorbidity can occur and might be contributed to several other factors as described above.

1. Araújo SA, Moreira DR, Veloso JM, Silva JO, Barros VL, Nobre V. Fatal Staphylococcal infection following classic Dengue fever. The American journal of tropical medicine and hygiene. 2010 Sep 1;83(3):679-82.
2. Oliveira JF, Burdmann EA. Dengue-associated acute kidney injury. Clinical kidney journal. 2015

Dec 1;8(6):681-5.

Question-1: in TABLE3 hematocrit > 20% , is this means Hct rising >20% from the baseline?  
If yes, it means that there were 5 out of 8 cases in fatal group with Hct.20% but it was stated that only 2/8 had DHF. Rising Hct>20% is 1 of the clinical criteria of DHF.

Answer-1: Respected reviewer, we agree that hematocrit >20% from baseline is considered as one of the clinical criteria of DHF. However, raised hematocrit is not only criterion and there are many other conditions that should be fulfilled in order to classify DHF. World Health Organization (WHO) criteria on dengue classification recommend that DHF should be diagnosed on account of fever, hemorrhagic manifestations, plasma leakage, thrombocytopenia and Hct rise ( $\geq 20\%$ ) (Reference 1, given below). According to these recommendations, presence of Hct  $\geq 20\%$  is not always necessary to be linked with DHF. As in previous investigations, Hct  $\geq 20\%$  has also been reported in DF where Ayub et al reported the presence of Hct  $\geq 20\%$  in 10 patients (2 patients with DHF and 8 patients with DF) (Reference 2, given below). In another case series, authors reported that Hct rise was more prominent (Average Hct = 50%) in DF during hospitalization as compared to DHF (Reference 3, given below). The guidelines by WHO describe hematocrit rise may be found in classical DF as a consequence of dehydration associated with high fever, vomiting, anorexia and poor oral intake. These might be possible reasons of increased hematocrit among these patients in our study. Moreover, the parameter Hct  $\geq 20\%$  is confounded by the availability of baseline values and variations in cut off Hct levels in different countries. Furthermore, interpretation of Hct may be difficult when there are confounding factors such as hemorrhage, excessive fluid replacement or in haemodilutional state. Therefore, most of the times the plasma leakage is also estimated by other measures (haemodynamic instability, fluid accumulation in extravascular space or hypoproteinaemia) or pre-set indicative values of Hct. For example, in Malaysia hematocrit values of 46 % ( $\leq 60$  years) or 42% ( $> 60$  years) for male and 40 % for female were suggested for cut-off value to suspect plasma leakage. Though, three fatal cases in our cohort had Hct > 20% but they did not fulfill other criteria of DHF, hence they were placed in the classification of DF. However, recovery of Hct levels was abrupt among these patients after fluid resuscitation. We would also like to add that sometimes Hct levels  $\geq 40\%$  were considered as diagnostic criteria of DHF (Reference 4, given below). In accordance with the objectives of our study, we recommend that patients with baseline raised Hct should be considered as high risk patient for death. We believe that dengue infection from last five years is presenting with specific trend and varying clinical pattern resulting in changed disease epidemiology that require time to time revisions of diagnostic criteria.

1. WHO/SEARO Guidelines: [http://apps.searo.who.int/pds\\_docs/B4751.pdf?ua=1](http://apps.searo.who.int/pds_docs/B4751.pdf?ua=1)
2. Ayyub M, Khazindar AM, Lubbad EH, Barlas S, Alfi AY, Al-Ukayli S. Characteristics of dengue fever in a large public hospital, Jeddah, Saudi Arabia. *J Ayub Med Coll Abbottabad*. 2006 Apr;18(2):9-13.
3. Saqib MA, Rafique I, Bashir S, Salam AA. A retrospective analysis of dengue fever case management and frequency of co-morbidities associated with deaths. *BMC research notes*. 2014 Apr 1;7(1):205.
4. Phuong CX, Nhan NT, Kneen R, Thuy PT, Van Thien C, Nga NT, Thuy TT, Solomon T, Stepniowska K, Wills B. Clinical diagnosis and assessment of severity of confirmed dengue infections in Vietnamese children: is the World Health Organization classification system helpful?. *The American journal of tropical medicine and hygiene*. 2004 Feb 1;70(2):172-9.

Question-2: In table 4, 4 cases of fatal group had pleural effusion, which is also the clinical criterion of DHF. Six cases had shortness of breath which is unusual in DF.

Answer-2: Respected reviewer, we again check SPSS data to verify these findings. We are extremely sorry that there were mistakes this regard. Both pleural effusion and shortness of breath was present

in two DHF cases. We have corrected this information in the table 4. Thank you so much for pointing out this error from the manuscript. By considering this mistake, we have checked and verified all the data lay within the manuscript.

Question-3: MODS is very unlikely to occur in DF.

Answer-3: Respected Reviewer, we agree that MODS rarely occur in DF and are more profound among patients with DHF or DSS. However, WHO regional office for South East Asia (SEARO) has issued contemporary guidelines on the management of dengue infection where MODS were termed as “expanded dengue syndrome” (EDS). These guidelines describe that there has been increasing reports of EDS or MODS not only in DHF but also in DF and it might be attributed to the geographical spread of dengue illness with more involvements of adults. Reference of these guidelines is given below (reference 1, given below). From last 4 years, Malaysia is experiencing a shift in dengue pattern with involvement of organ systems including heart, lungs, brain and kidney. Recently in 2015, this issue was highlighted by ministry of health Malaysia (reference 2, given below); however, reason behind this is yet to be determined. It might be possible that MODS in DF in our study are attributed to the geographical spread, changing epidemiology and varying disease pattern of dengue infection. In addition, it might also be associated to antigenic shift of dengue virus but further studies are required to determine the possible mechanisms. According to health ministry Malaysia, similar situations have also been experienced by neighboring countries such as Singapore and Thailand (reference 2, given below). Moreover, change in disease epidemiology can be understood by the fact that renal involvements were previously thought to be associated with DHF/DSS, but recently it was also reported in patients with DF (reference 3, given below). Nevertheless, in vivo studies have previously reported that dengue virus can affect almost all the organs of the body (reference 4, given below). Dengue virus has broader tropism and can replicate in hepatocytes, glomeruli, type II pneumocytes, cardiac fibers, monocytes or macrophages and endothelial cells leading to MODs (Reference 5, given below). EDS or MODS in DF have been reported in the literature (Reference 6, given below). We hope that these explanations support our findings and satisfy the concerns of reviewer-1.

1. WHO/SEARO Guidelines: [http://apps.searo.who.int/pds\\_docs/B4751.pdf?ua=1](http://apps.searo.who.int/pds_docs/B4751.pdf?ua=1)
2. <http://www.themalaymailonline.com/malaysia/article/question-marks-as-organ-failure-joins-symptoms-of-dengue-fever>
3. Khalil MA, Sarwar S, Chaudry MA, Maqbool B, Khalil Z, Tan J, Yaqub S, Hussain SA. Acute kidney injury in dengue virus infection. *Clinical kidney journal*. 2012 Oct 1;5(5):390-4.
4. Noisakran S, Onlamoon N, Songprakhon P, Hsiao HM, Chokephaibulkit K, Perng GC. Cells in dengue virus infection in vivo. *Advances in virology*. 2010 Aug 12;2010.
5. Póvoa TF, Alves AM, Oliveira CA, Nuovo GJ, Chagas VL, Paes MV. The pathology of severe dengue in multiple organs of human fatal cases: histopathology, ultrastructure and virus replication. *PloS one*. 2014 Apr 15;9(4):e83386.
6. Assir MZ, Jawa A, Ahmed HI. Expanded dengue syndrome: subacute thyroiditis and intracerebral hemorrhage. *BMC infectious diseases*. 2012 Oct 3;12(1):240.

Question-4: The institution of the 4th author Adnan in the title page and in page 1/40 are not the same. Keywords in these 2 pages are also different.

Answer-4: Respected reviewer, the institution of 4th author (Adnan AS) and Keywords have been corrected in the manuscript file as well as in Online Submission system. Thank you so much for pointing out this error.

Respected reviewer, we tried our best to address all your concerns. Please let us know if any other things or corrections are required. We shall be very thankful to you.

REVIEWER-2

Reviewer Name: Dr. Kandati Jithendra

Institution and Country: Narayana Medical college, Chinthareddypalem, Nellore, Andhra pradhesh, India.

Comment-1: Good work done by the authors.

Response-1: Respected reviewer, thank you so much for appreciating and acknowledging of work. We all authors are extremely thankful to you for your time and efforts contributed to review this manuscript.

REVIEWER-3

Reviewer Name: Dr. Erum Khan

Institution and Country: Aga Khan Univerisity, Karachi, Pakistan

Please state any competing interests or state 'None declared': none

Comment-1: A well written report, addresses the critical question of what factors that determine the severity of patients with dengue infection especially in an outbreak situation.

Response-1: Respected reviewer, thank you so much for appreciating and acknowledging our work. We all authors are grateful for your time and efforts to review this manuscript.