

5 April 2021

Respected Sir/Madam

Reference#: 04611317

Title: Dengue Hemorrhagic Fever and the Liver

I am hereby giving point response to your comments;

Reviewer #1

Comment #1: In the section: "IMMUNE MEDIATED HEPATOCYTE INJURY AND CYTOKINE STORM", the authors have not sufficiently addressed the cytokines that are involved according to the literature and their effect as mediators in Dengue Hemorrhagic Fever and the Liver. TNF is not the only cytokine involved in DHF.

-Guabiraba R, Ryffel B. *Dengue virus infection: current concepts in immune mechanisms and lessons from murine models. Immunology. 2014;141(2):143-156.*

-Wan, SW., Wu-Hsieh, B.A., Lin, YS. et al. *The monocyte-macrophage-mast cell axis in dengue pathogenesis. J Biomed Sci 25, 77 2018)*

As this is a review, it is not enough to state: "This phenomenon could promote a severe inflammatory response with numerous cytokine released as cytokine storm". This should be elaborated.

Author answer: I already added the cytokines that are involved in dengue hemorrhagic fever and the liver as suggested and highlighted.

Comment #2: As kupffer cells are not the only cells that relevant in DHF-induced liver damage but there are indications for the involvement of monocyte and mast cells as well, mainly monocytes have been recognized as major targets of DENV infection, the authors should address and elaborate about these immune cells and cite the relevant papers.

-Wan, SW., Wu-Hsieh, B.A., Lin, YS. et al. *The monocyte-macrophage-mast cell axis in dengue pathogenesis. J Biomed Sci 25, 77 2018*

-Kala Jessie, Mun Yik Fong, Shamala Devi, Sai Kit Lam, K. Thong Wong, *Localization of Dengue Virus in Naturally Infected Human Tissues, by Immunohistochemistry and In Situ Hybridization, The Journal of Infectious Diseases, Volume 189, Issue 8, 15 April 2004, Pages 1411–1418*

Author answer: I already addressed and elaborated about these immune cells and cited the relevant papers as suggested and highlighted.

Reviewer #2

Comment #1: Needs some language refinement.

Author answer: I already checked the English grammar again and refined them.

Comment #2: Is this statement correct Line 69 - Hepatic injury in DVI is more common in DHF than DF. Did authors mean abnormal liver test / as hepatic injury should be worse with hemorrhagic fever?

Author answer: From "Wahid SF, Sanusi S, Zawawi MM, Ali RA. A comparison of the pattern of liver involvement in dengue hemorrhagic fever with classic dengue fever. Southeast Asian J Trop Med Public Health. 2000 Jun;31(2):259-63. PMID: 11127322." Showed that "There were more (60%) DHF

patients with hepatomegaly compared to DF (40%). Analysis of the liver profile showed that liver dysfunction was commoner in DHF compared to DF, indicating that the degree of liver impairment may be related to the severity of DHF.”

Comment #3: Please discuss separately DEN in patients with existing liver disease - See Kulkarni et al. J Clin Transl Hepatol. 2019 Jun 28; 7(2): 106–111.

Author answer: I already added the discussion as suggested and highlighted.

Comment #4: Discuss DEN with respect to acute on chronic liver failure. Please see Jha et al Indian J Gastroenterol . 2013 Mar;32(2):108-14.

Author answer: I already added the discussion as suggested and highlighted.

Comment #5: Discuss current data on liver transplantation for dengue liver failure Include 2 diagrams - one showing dengue pathophysiology, the other showing dengue effects on the liver.

Author answer: I already added the discussion as suggested and highlighted.

Best regards,

Assoc.Prof.Wattana Leowattana