Author’s response to reviews

Title: Severity of acute hepatitis and its outcome in patients with dengue fever in a tertiary care hospital Karachi, Pakistan (South Asia):

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Author’s response to reviews: see over
Covering letter

Dated 15th December 2009

To

Dr Rikki Graham PhD
The BioMed Central Editorial Team

Subject: Revised Comments for

MS: 2523688802666021
Severity of acute hepatitis and its outcome in patients with dengue fever in a tertiary care hospital Karachi, Pakistan (South Asia): An Analytic cross sectional study.
Om Parkash, Aysha Almas, Syed Hasnain Alishah, SM Wasim Jafri, Saeed Hamid and Jaweed Akhtar.

Please see my responses to comments made by reviewers

For Reviewer: Dorothea Nitsch

Thank you very much for valuable comments.

Regarding study design, yes we do agree with the reviewer’ point of view of this being a cohort study henceforth we have modified cross sectional into cohort study design which actually was.

Yes we have followed this cohort for the primary outcome measures i-e in hospital mortality and length of stay only.

Comments for points made by reviewer

- Yes, We do Dengue IgM in every patients in whom clinical suspicion of dengue fever is high who have short history of fever and Dengue IgM was done in every patient. As it is clear in our study that the mean duration if fever was 6 days. Dengue IgM is done uniformly in the same hospital laboratory with same methodology.

- Yes, ALT was done in all patients in this cohort. This was done in same hospital laboratory and methodology was uniform.

- We have excluded the patients with established chronic liver disease or the hepatitis virus like Hepatitis B or C as they can confound our results. We had excluded total of 16 patients with other serology positive.
Yes all patients with dengue fever were consistently checked for ALT at the time of admission. And methodology was same for all patients since it was done at same hospital lab.

Regarding the point of diagnosis of hepatitis based on ALT level. Yes word hepatitis means an inflammation/injury of liver which is picked by transaminase level. The aminotransferases (transaminases) are sensitive indicators of liver cell injury and are most helpful in recognizing acute hepatocellular diseases such as hepatitis. They include the aspartate aminotransferase (AST) and the alanine aminotransferase (ALT). The aminotransferases are normally present in the serum in low concentrations. These enzymes are released into the blood in greater amounts when there is damage to the liver cell membrane resulting in increased permeability. (References are (1). Harrisons 17th edition, chapter 296 and (2). American Gastroenterological Association Medical Position Statement: Evaluation of Liver Chemistry Tests. GASTROENTEROLOGY 2002;123:1367–1384.)

Since these concurrent liver problems will confound the main outcome of our study so we have excluded them. I don’t understand that this would give any kind of false impression to the local doctors for the patients with dengue fever hepatitis

Since now this study has been changed to cohort study as rightly suggested by the reviewer. In our study clock started when patient with dengue fever got admitted with raised ALT level and has been categorized into mild to moderate hepatitis and severe hepatitis based on admission level of ALT. The clock stopped in our study at the time of discharge or at death of patient in hospital. We think that it was systemically approached as reviewer has commented in this point.

We had predefined the acute renal failure that any serum creatinine greater than 3 times of normal value will be taken as acute renal failure. Yes Ideally eGFR should have been checked for these patients to have a better idea to estimate acute renal failure/injury. So far in our country there is no validated equation to determine the renal failure so majority of the published studies from our country are based on rise in serum creatinine level above the normal. Recently one of the study published from Pakistan (Reference: Etiology of acute renal failure in a tertiary center. Saudi J Kidney Dis Transpl. 2008 Nov;19 (6):1009-14.

Management in our center is very consistent since all these patients get admitted in same ward of hospital and under internist care. We had used same proforma for all patients. Uniform charts were used for all patients in department of medicine with dengue fever in same ward. All the blood tests and radiological workup is consistent throughout. Our institute is the only JCIA accredited institute in our country because of the maintenance international standards and quality of care.
Regarding point of study size, we had mentioned the precision (bond on error) and CI not alpha error. And we had given assumption of sample size i-e prevalence. We could not find the mortality figures associated with dengue hepatitis hence we could not give exact figure of difference in mortality in dengue hepatitis. We had done power calculation by hypothesizing (alternate hypothesis) that overall mortality with dengue fever hepatitis would be higher, though we had not exact figures for mortality associated with dengue hepatitis. Based on this hypothesis sample size was much smaller than the given sample in the study. We had taken larger sample size that is given in text.

Regarding the point of skewed data, description of data summary has been amended and used the median and IQR for non normally distributed variables (like median ALT of 88.50 IU/L; IQR 43.25-188 IU/L etc)

Regarding the assumptions of cox regression: We have tested the Proportion Hazard (PH) assumption and fulfilled. We have checked by making interaction term between log of time variable with other covariates (exposure).

Regarding point of deleting the segment of hepatotropic viruses, since we meant to say only viruses not bacteria and Leptospirosis, which is bacterial infection; is very rare entity in our country.

For Reviewer: Fransisco Souto

Thank you very much for highlighting this point and we have amended the manuscript as suggested by the reviewer.

I think this is good point but hepatitis term can be used as this has been used in gastroenterology and medicine literature as well. The aminotransferases (transaminases) are sensitive indicators of liver cell injury and are most helpful in recognizing acute hepatocellular diseases such as hepatitis. They include the aspartate aminotransferase (AST) and the alanine aminotransferase (ALT). The aminotransferases are normally present in the serum in low concentrations. These enzymes are released into the blood in greater amounts when there is damage to the liver cell membrane resulting in increased permeability. (References are 1. Harrisons 17th edition, chapter 296, and 2. American
For Reviewer: Mei-Chuan Kuo

➢ Regarding the uniformity in writing the result units, changes have made as suggested by the reviewer.

I am extremely thankful for the reviewers for highlighting the importance of this article and has put their efforts to study this article and for giving very valid suggestion. So this article has undergone revisions as suggested by reviewers and I hope this will satisfy the editorial board of the journal now.

Sincerely

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