Reviewer’s report

Title: 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.

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Reviewer: Dorothea Nitsch

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Review of 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.; Dr Om Parkash et al.

This is a paper that wanted to look at the features of patients with Dengue infection admitted to their hospital. This is a study that is retrospectively reviewing case-notes and extracting information on patients, and I believe that the authors interpreted this as a cross-sectional study, because they looked at patients 'in a snap-shot'.

However, in epidemiological terms, what they have done, is to identify a cohort of in-patients and follow them up:

'All inpatients of age > 14 years who had history of fever, positive dengue IgM and whose ALT were done, were included in the study.', and they then looked at their survival afterwards. Survival analysis is only possible if you have followed up people over time. If this time-element of follow-up is present, epidemiologists do call this a cohort study design. So I would advise to call this a cohort study throughout. If the follow-up had been absent, then this would have been a cross-sectional study.

I will go through the features of the study point by point:

The authors have to clarify much more their service methods to patients who are admitted with fever:

=> Is everybody tested for Dengue fever using IgM antibodies?

if yes, then this is fine, if no, then they will perhaps have selection bias at the outset, and not a representative picture of all those who have Dengue fever. If testing for Dengue is not done uniformly, authors have to convince us how they ensured that they did not miss dengue fever cases.

=> A similar question applies for ALT testing. If testing is not done uniformly, then they might have a very select group of Dengue patients (i.e. selected towards a suspicion of liver injury, see also below), and not a representative picture.

=> Exclusion of patients with other forms of liver disease already at baseline will
bias the picture. At this stage it is about getting everybody who has Dengue into
the study. If they have another infection at admission (e.g. Hep C) then they still
are patients with Dengue worth looking at. Could the authors clarify how many
patients they excluded because they had a liver problem due to another disease
at start? This exclusion will again bias the study.

'... we aim to assess the frequency of hepatitis in dengue infection.

=> Please see my point to the issue of ALT testing and exclusion of patients as
outlined above. Only if all patients with Dengue fever were consistently tested,
then they get representative frequencies at baseline. If there is selection to start
with they have a cross-section of patients at baseline that is biased towards high
rates of elevated ALT.

=> I am not a hepatologist or gastroenterologist- but to my knowledge I don't
diagnose hepatitis just with ALT. The authors need to clarify how they confirmed
their diagnosis.

=> if there are concurrent other liver problems at baseline then it is important to
describe them, rather than excluding these patients - this will introduce bias and
give a wrong impression of what doctors in Karachi have to deal with.

'We also aim to compare their outcome (mortality,length of stay and
complications) between patients with mild to moderate and severe hepatitis in
dengue infection.'

=> this type of question is what makes this study a cohort study (please see
above). Now, for doing this analysis correctly, there is the need to identify
correctly all people with hepatitis and distinguish them from others. It is also
important to think about when the clock for risk associated with hepatitis starts
ticking... is it when the ALT is slightly elevated, or three times as much? What
about patients who initially don't have a liver problem but then go into septic
multiorgan failure a day after admission with then a liver problem - would the
clock start ticking at time of admission or afterwards? When did the clock stop
ticking - when they left hospital or died? From what was written I am not sure that
a systematic approach was taken.

=> re other complications: 'Renal Failure (ARF) was defined as rise of creatinine
(Cr) >3 times of baseline.' How can you calculate renal failure if patients don't
have baseline creatinines because they come in septic shock with renal failure?
If they had only one time point at which they had measured creatinine, then I
would suggest using the MDRD equation to estimate glomerular filtration rate
based on serum creatinine. This equation is not brilliant in South Asian patients
but the authors could define those with eGFR<30 as having a functional kidney
impairment (which is quite severe kidney impairment and unlikely to be biased by
the equation used).

Now, if management of patients is very consistent, then these questions above
can all be answered. If recording of what happened is poor, or if patients are
tested for problems in an irregular fashion based on doctor’s perceptions then
half of the data are absent, and this study won't give us representative and
accurate information.
Regarding study size:
'Ve required a minimum sample size of 350 patients by assuming the 35% prevalence of liver dysfunction in patients with dengue fever, with 0.05 bound on error and 95% confidence level.(11)'

=> This sentence is definitely not written by somebody who understands statistics - a 0.05 alpha implies that 95% confidence intervals will be calculated, typically power calculations are done for a fixed alpha and for a given effect size and a given power. I am not clear what the power will be. I am not sure which is the main question they wanted to address with their sample size calculation- for what did the researchers power:
- to find a given prevalence of hepatitis with a given accuracy?
- or to find an association with mortality? If yes, how big was the difference in outcome they were powering for?
I would not request power calculations for a descriptive study if there are no prior data on the problem. Somewhere one has to start. However I would request to be very systematic in the approach to collecting data to really describe the problem, and I am not convinced that has been done.

Regarding statistical analyses:
'Results are presented as mean + standard deviation (SD) for continuous variables'

=> The descriptive analyses of continuous variables in this way are only meaningful if the variables were normally distributed. If data were skewed (i.e. non-symmetric around the mean), then perhaps other measures (e.g median, upper and lower quartile values) might be more meaningful descriptors of the summary data.

', frequency and percentage are given for qualitative variables. Chi square test was used to compare categorical variables and fischer exact test where applicable. Student t test was used to compare continuous variables.'

=> This is all fine in terms of methods. If continuous data were skewed a t-test is perhaps not ideal and non-parametric tests should be used. I am surprised that the authors have no missing data - how did they deal with missing information?

'In survival analysis cox proportion hazard ratio (Cox regression) was determined for mortality in DHF/DSS and severe hepatitis.'

=> how did the authors test that the assumptions of the Cox regression were satisfied?

'Conclusions: ....Dengue fever should be considered when liver functions are deranged apart from routine hepatotropic viruses.'

=> I would suggest to delete 'apart from routine hepatotropic viruses', because dependent on the setting there are also bacteria (e.g. Leptospira) that cause a
very similar clinical picture.

I believe this paper reflects a fair bit of reviewing of case notes. Unfortunately it needs some more work. Readers need to better understand whether this is a representative study of in-hospital patients or not.

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

no competing interests