Author’s response to reviews

Title: Elevated D-dimer is Associated with Increased 28-day Mortality in Acute-on-Chronic Liver Failure in China: a Retrospective Study

Authors:

Tingting Qi (tingtingqi@126.com)
Congyan Zhu (284146953@qq.com)
Jun Hao (1410830602@qq.com)
Qinjun He (598637358@qq.com)
Yongpeng Chen (cy@fimmu.com)
Fuyuan Zhou (fuyuan@smu.edu.cn)
Jinlin Hou (jlhousmu@163.com)
Jinjun Chen (chjj@smu.edu.cn;2732589916@qq.com)

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Author’s response to reviews:

Dear editor,

It is our pleasure to receive your decision and advice on our manuscript “Elevated D-Dimer is Associated with Increased 28-day Mortality in Acute-on-Chronic Liver Failure: a Retrospective Study.” (BMGE-D-18-00230R1). We also appreciate the comments and suggestions from the reviewers.

We have improved the manuscript according to the comments and suggestions of the reviewers. The detailed point-by-point responses are listed below. We wish these improvements in our revised manuscript will satisfy editors and reviewers.

Sincerely yours,

Jinjun Chen
Technical Comments:

List of Responses

Jun Chen (Reviewer 1): In this manuscript, Jinjun Chen et al. revealed a nonlinear relation between D-dimer level and 28-day mortality with a turning point at 6.5 mg/L FEU in ACLF. Statistically, they calculated odds ratios of D-dimer level for risk of 28-day mortality by logistic regression analysis with non-adjusted and multivariate-adjusted models. They demonstrated that D-dimer was associated with short-term prognosis. In my opinion, this article offers a quotable experience in predicting short-term prognosis in ACLF patients. However, there are some minor deficiencies.

1. The authors mentioned that D-dimer levels positively correlated with all conventional prognostic predictive scores (MELD, MELD-Na, CLIF-OF, CLIF-C Ads, CLIF-C ACLFs), but not explored and compared the value of the latter's in predicting prognosis of ACLF patients.

Author response: We added ROC curve analysis of D-dimer in predicting 28-day mortality and compared the area under curve with MELD, MELD-Na, CLIF-C ADs and CLIF-C ACLFs and found no significant differences between D-dimer and these conventional prognostic scores in predicting 28-day mortality (Fig.3). (page 10, line 203-208)

2. In this single-center retrospective study, it's special that the vast majority of the ACLF patients had HBV related chronic liver disease, other than NASH, HCV, and other liver disease in West. It is appropriate to highlight "in China" in the title and abstract, which is conducive to understanding of global readers.

Author response: We updated both title and abstract with additional text such as “in China” as suggested. (page 1, line 2; page 2, line 41).

3. The cut-off value of D-dimer lever (6.5 mg/L FEU) was identified as the turning point of the adjusted smoothed plots in Figure.3. So, marking out the precise location of the turning point would be appropriate. In addition, the authors compared the clinical data of the patients with less D-dimer lever and high D-dimer lever in Table.1. they should illustrate how to group all patients in the beginning of the Results.

Author response: 1) We added an auxiliary line at x=6.5 to mark out the turning point in Figure 4, which hopefully will make it more clearly for readers. 2) The turning point of D-dimer=6.5 were calculated based on smoothing plot as we illustrated in Figure 4 and table 3. To avoid
confusion, only overall patients’ characteristics were showed in table 1 in this revised manuscript (page 18-21, line 392). The comparison between cases with different D-dimer levels was shown in additional file 1 (table S2) (additional file 1, page 4-6, line 5-6).

giovanni capretti (Reviewer 2): Dear authors,

first I want to thank you for the opportunity to review your interesting work.

You clearly state the drawbacks of your study design and consider them in your conclusions; this in my opinion is of a paramount importance in any proper scientific paper.

Still your work, as it is, can raise some questions:

- of your 192 patients that meets the APASL ACLF criteria 65 were excluded because the D-Dimer wasn't measured at the admission. 34% is a big percentage of lost cases. You should provide an analysis or demonstrate that this patients were theoretically similar to the cohort you analyzed; otherwise you could have a fundamental selection bias. I provide you an example, if the 65 cases without the d-dimer are the ones admitted in a specific clinical setting or in specific condition or peculiar clinical scenarios this can mislead you evaluation providing the data of a subpopulation and not on your real patients' population

Author response: We added a supplementary table to compare baseline characteristics and short-term prognosis between 115 cases included in the study and 65 excluded cases due to lack of D-dimer measurement (Additional file 1, Table S1). Baseline characteristics and 28-day prognosis of patients without D-dimer test at admission were roughly comparable with those included cases, expect for lower proportion of hepatic encephalopathy, cerebral failure and the proportion of subjects diagnosed with EASL-ACLF. However, according to our subgroup interactions analysis (table 4), the odds ratios for patients with and without encephalopathy were 1.1 (0.7, 1.6) and 1.6 (1.1,2.3), and we detected no significant subgroup interactions between these two groups. Subgroup analysis among patients with and without EASL-ACLF was similar. Therefore, these excluded cases had limited impact on the evaluation of independent effect of D-dimer on 28-day outcome (Additional file.1, page 1-3, line 1-2).

- of great support to your conclusions could be an external validation cohort of your findings or at least and internal one (e.g. with a bootstrap).

Author response: An internal validation and/or external validation is always necessary when developing a diagnostic or prognostic prediction model. As we stressed in the discussion section, for now D-dimer tested results are not comparable among various assays. Therefore instead of establishing a predictive model, the aim of current study was to figure out the relationship between fibrinolytic marker D-dimer level and 28-day outcome in ACLF patients. Still, to illustrate the prognostic value of D-dimer alone for 28-day outcome, we added a ROC curve analysis with a bootstrap validation (Fig. 3, page 10, line 204-208). We hope the measurement of
D-dimer can be standardized in the near future or other surrogate marker related to fibrinolytic would help to establish a more accurate prognostic model.

- 115 cases could statistically support an extended multivariate analysis such as your adjusted models; I have some concerns if the evaluations of adjusted Odds ratios for 28-day mortality per unit increase in D-dimer in subgroups of patients could still have any statistical validity. In some cases you performe a multivariate analysis on subpopulation of 30 or less patients

Author response: We admitted that it was not sufficient to illustrate the definite independent effect of D-dimer in each subgroup due to the limited sample size. However, because ACLF is a highly heterogeneous syndrome, subgroup analysis was necessary as a sensitivity analysis to detect potential interactive roles in the association between D-dimer and 28-day outcome. Despite most odds ratios of D-dimer didn’t reach statistically significance, especially in adjusted models, these data suggested that D-dimer was a risk factor in all subgroups (OR>1.0), and no interaction effect was detected in current cohort. Further studies with larger sample size are warranted to confirm the role of D-dimer in particular subgroups of ACLF patients (page 11, line 228-231; page 23-24, table 5, line 408-415).

- the D-Dimer levels correlate in your analysis with a wide spectrum of severity scores and prognostic elements. Have you performe any test to assess how much it's measure can add to the already present elements/scores?

Author response: When including only D-dimer and any of these conventional prognostic scores in logistic regression analysis, D-dimer remained an independent risk factor. However, as we demonstrated aforementioned, in the current study, it was not appropriate to establish a prognostic model based on D-dimer due to the limitation of methods of D-dimer test, and lack of external validation cohort. Still, in the revised manuscript, we compared the areas under curves of D-dimer alone with conventional prognostic scores and found no significant differences (Fig. 3, page 10, line 204-208).