Author's response to reviews

Title: Prognosis of critically ill cirrhotic versus non-cirrhotic patients: A comprehensive score-matched study

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Version: 5
Date: 25 September 2014

Author's response to reviews:

Reviewer 1: Kevin Zhao

• Discretionary Revisions

1) In the abstract and results section, it states that a total of 336 critically ill patients were enrolled. However, the study has 174 patients in the APACHE III arm and 110 patients in the SOFA arm (total of 284). Please mention why 52 patients were excluded.

Answer: The cases were first stratified by the clinical scores using the SAS SURVEYSELECT Procedure, and the samples were then selected by simple random sampling within the desired strata. 336 critically ill patients were enrolled in the database, however, not all of the patients can be matched. Finally 52 patients were not able to be matched, so they were excluded.

2) Could you include in the methods section how your study accounted for mortality in the length of stay data? I find it interesting that the non-cirrhotics in the APACHE-III matched group had a 14% lower mortality than cirrhotics, but non-cirrhotics had a increased ICU length of stay by 5 days.

Answer: The length of stay data included patients with in-hospital mortality. The shorter overall ICU length of stay of cirrhotic patients was attributed by the higher hospital mortality. We'll address this in the method section, as “The ICU and hospital length of stay data included those from patients with hospital mortality”. Thank you for the kind notice.

3) On page 12, line 13, the study contends that “renal function plays a critical role in the outcomes of critically ill cirrhotic patients, and also supports that the RIFLE
classification is independently associated with the outcomes of critically ill cirrhotic patients. While I understand the premise of that statement, I don't see specific data that draws that conclusion. I don't see a direct comparison of cirrhotics with and without renal disease on patient outcomes. Perhaps I am misreading the data, but Figure 2A and 2B argue that RIFLE classification results in poorer overall outcomes across ALL ICU patients, but does not make the argument that it specifically covers cirrhotics.

Answer: Thanks for your kind notice. Indeed, this study didn't specifically analyse the impact of RIFLE classification to the outcome in cirrhotics and non-cirrhotics. We'll eliminate the following paragraph “Therefore, cirrhotic patients with higher de novo SOFA scores should have better results in the RIFLE classes to maintain similar SOFA scores as those of non-cirrhotic controls. This result indicates that renal function plays a critical role in the outcomes of critically ill cirrhotic patients, and also supports that the RIFLE classification is independently associated with the outcomes of critically ill cirrhotic patients [9]. We'll replace it with “The cirrhotics tend to have malnutrition, low muscle mass and impaired synthesis and creatinine. Therefore, the RIFLE classification, which is based on serum creatinine and urine output, may lead to underestimation of AKI severity and overall illness."

4) In stating that SOFA is superior to APACHE III, the authors contend that MAP, GCS, and RIFLE classification play critical roles. While those categories in tables 2 and 3 are statistically different, there are other statistically significant differences as well, such as albumin, Hb, HCO3. Are those worth mentioning as well?

Answer: Thanks for your kind suggestion. In table 3, the albumin level was also significantly different between cirrhotics and non-cirrhotics. We'll address this in this result.

5) It may be worth mentioning that a large difference between APACHE III and SOFA-matched data is the % of patients in shock. While both tables note statistically significant differences (cirrhotics less likely to be in shock than non-cirrhotics), the difference is quite remarkable. There is a 13.8% difference in the APACHE-III matched group while there is a 38.2% difference in the SOFA-matched group.

Answer: In both APACHE III and SOFA-matched groups, the non-cirrhotic patients had significantly higher rate of shock compared to cirrhotic patients. This was because that the main reason of ICU admission was mainly hepatic failure in cirrhotic patients, and GI bleeding and sepsis in non-cirrhotic patients. This will be addressed in the result section.

6) I would like to see more emphasis and explanation in the discussion on why SOFA is a superior to APACHE III for prognosticating cirrhotics.

Answer: Thank you for your kind suggestion. The following paragraph will be added in the discussion section “As shown in table 4, in APACHE III-matched group, the SOFA score had better discrimination ability in cirrhosis than non-cirrhosis patients (AUROC 0.810 ± 0.056 vs. 0.624 ± 0.060). The SOFA score is also simpler for clinician to assess. Therefore, SOFA score is
recommended for prognosis prediction in cirrhotic patients, with cut-off value 10 points providing the optimal overall correctness. On the other hand, both SOFA and APACHE III scores are comparable in non-cirrhotic patients.”

Reviewer 2: Laleh Jalilian

Major Compulsory Revisions:

1- It is unclear to me how the authors divided their initial population into the APACHE-III and SOFA groups and then how they matched the cirrhotic and non-cirrhotic patients in the groups. Did they utilize a random system that allowed them to divide and match the patients in a way such that bias was not introduced?

Answer: The cases were first stratified by the clinical scores using the SAS SURVEYSELECT Procedure, and the samples were then selected by simple random sampling within the desired strata.

2- The study design compares the ability of APACHE III, a prognostic model, to predict mortality vs SOFA, an organ dysfunction score that quantifies the burden of organ dysfunction. The authors do not touch on the fact that prognostic scoring systems like APACHE are concerned with predicting mortality, whereas organ dysfunction scores like SOFA better describe morbidity. Prognostic scoring models like APACHE III assume that mortality is affected by physiologic disturbances that occur early in the course of illness, whereas organ dysfunction scoring systems like SOFA allow determination of organ dysfunction at the time of admission and at regular intervals throughout the ICU stay, thus allowing for assessment of the change in organ function. The accuracy of mortality predictions may be improved with repeat measurements with organ dysfunction scoring systems like SOFA. While the authors have taken data only from the first day of ICU admission both for APACHE and SOFA groups and have used that in their analysis, they do not mention that one additional benefit of using a scoring system like SOFA is that it allows for sequential measurements. This better reflects the dynamic aspects of disease processes and may provide better information on mortality risk. This could be an additional support for their conclusion that SOFA is a better and easier-to-implement model for predicting mortality in cirrhotic patients.

Answer: Thank you for this wonderful suggestion. We'll address this in the discussion section as your suggestion.

3- In the Results Section, Subject characteristics, the authors write in the second paragraph, “In the SOFA-matched group (Table 3), the cirrhotic patients had lower platelet counts (p <0.001), a better Glasgow coma scale (GCS), better hemodynamic status, worse renal function, and a higher bilirubin level than the non-cirrhotic patients.” I’m assuming the authors made a mistake when they write “worse renal function.” Perhaps they meant “better renal function,” since they, later in several places in the paper, state that renal function in the cirrhotic group is better. For instance, the authors show in Table 3 that serum creatinine for the non-cirrhosis group is 3 vs 1.8 for the cirrhosis group. Furthermore, the RIFLE for non-cirrhosis group is 1.9, and 1.4 for the cirrhosis group. In addition, the authors later write “The RIFLE classes, however, showed better results in cirrhotic
patients than in non-cirrhotic controls \( (p = 0.041) \) in the SOFA-matched group. Therefore, cirrhotic patients with higher de novo SOFA scores should have better results in the RIFLE classes to maintain similar SOFA scores as those of non-cirrhotic controls.”

Answer: Thanks for your correction. The “worse renal function” was corrected to “better renal function”.

4- In the Results Section, Mortality and Severity of Illness Scoring Systems, the authors write “In cirrhotic patients, a SOFA score had a similar predictive power as the APACHE III score. In contrast, the RIFLE system showed no inferior discrimination in the cirrhotic group.” I find the second sentence a bit confusing. Do the authors mean the RIFLE system showed no inferior discrimination when compared to the non-cirrhotic group, or that it had an inferior predictive power as compared to the SOFA and APACHE III scores? Please clarify.

Answer: Thanks for your kind notice. The sentence was modified as “SOFA score had a best predictive power”. To avoid confusion, the following sentence will be eliminated “In contrast, the RIFLE system showed no inferior discrimination in the cirrhotic group.”

5- In the Results Section, Mortality and Severity of Illness Scoring Systems, the authors write, “The RIFLE system had the highest specificity for prognostic prediction.” Could you be more specific in this sentence? For instance, I think you could further clarify the sentence by stating that the results demonstrate that the RIFLE system had the highest specificity for prognostic prediction in the cirrhotic group of both the SOFA-matched and APACHE III-matched groups.

Answer: Thank you for your kind suggestion, the sentence was modified as “The RIFLE system had the highest specificity for prognostic prediction in the cirrhotic group of both the SOFA-matched and APACHE III-matched groups.”

6- One of the outcomes of interest was ICU length of stay, in addition to hospital mortality and hospital length of stay, yet the authors don’t discuss this much in the discussion. For both the SOFA-matched and APACHE III-matched groups, the cirrhotic patients had significantly shorter length of ICU stay as compared to the non-cirrhotic patients. Do they attribute this to mortality and poorer short-term prognosis of cirrhotic patients, or do they attribute it to the characteristics of the non-cirrhotic patients?

Answer: Thank you for the suggestion. Indeed, the shorter overall ICU length of stay of cirrhotic patients was attributed by the higher hospital mortality. We’ll address this in the “result” section, as “In both APACHE III and SOFA-matched groups, the cirrhotic group had shorter overall ICU length of stay of cirrhotic patients. This was attributed by the higher hospital mortality of cirrhotic patients”.

Minor Essential Revisions:

1- In the acknowledgments, the “k” in the kidney of the Chang Gung kidney Research Center should be capitalized.

Answer: Thanks for your kind notice. The “k” was capitalized as your remind.

2- In Table 5, SOFA-matched group, APACHE III Total population Overall
Corectness (%) is currently written as 071. Please correct.
Answer: Thanks for your kind notice. The “0” was eliminated.

Discretionary Revisions:

1- In the “Background” section, the authors write, “however, detailed independent comparisons between APACHE III and SOFA scores have been performed in a limited number of studies.” Citations to these studies would be helpful for the readers.
Answer: Thanks for your kind suggestion. The citation was added.

2- In the “Definitions” section, the authors write, “Illness severity was assessed by the SOFA and the APACHE III scores, which were defined and calculated as described previously [1, 2].” This is a very minor suggestion, but I would suggest modifying the sentence to read “Illness severity was assessed by the APACHE III and SOFA scores, which were defined and calculated as described previously [1, 2],” which would make APACHE and SOFA be written in an order that is consistent with references 1 and 2.
Answer: Thanks for your kind suggestion. The sentence was modified as your suggestion.