Author’s response to reviews

Title: DEVELOPMENT OF A MORTALITY SCORE TO ASSESS RISK OF ADVERSE DRUG REACTIONS AMONG HOSPITALIZED PATIENTS WITH MODERATE TO SEVERE CHRONIC KIDNEY DISEASE

Authors:

Monica Danial (monicadanial83@gmail.com)
Mohamed Azmi Hassali (azmihassali@gmail.com)
Ong Loke Meng (onglokemeng@gmail.com)
Yoon Chee Kin (yooncheekin@gmail.com)
Amer Hayat Khan (dramer@usm.my)

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Author’s response to reviews:

Dear Esteemed Reviewers,

Firstly, thank you for your efforts for going through this manuscript and providing constructive comments as to enhance the value and readability of our manuscript. We have made substantial revisions to the manuscripts. And to best of our ability made all the substantial amendments as pointed out by the reviewers. As the main author of this manuscript, I really hope that this manuscript after the revisions will be accepted for publication as this is one of my first few attempts in publishing an article in medical field and if accepted it would provide encouragement to young researchers like me to publish in established journals.

All responses are highlighted in yellow in the manuscript and in this response letter.

Technical Comments:

Editor Comments:

When revising the manuscript, please consider the following:

1) Address all issues raised by referee #2 very carefully;

Response: Yes, we have addressed issues raised by referee #2 very carefully.
2) Explain the reasons why you selected each statistical test so that everything can be clear also to the non-experienced reader;

Response: Yes, explained (lines 126-127, lines 135-137, lines 141-143, lines 148-149).

3) Carefully proofread the final version for English style.

Response: Apologies for the many grammatical errors as English is not the Native language in Malaysia. Nevertheless, as to improve readability and flow of our manuscript, we have approached someone whom extensively publishes his articles in international journals to review this manuscript before submission.

Reviewer reports:

Rozina Hoque, MBBS, MPhil Pharmacology (Reviewer 1)

Your article is very much helpful in clinical setting.

Response: Thank you so much Dr Rozina Hoque.

1. Better to write in the following way ’28 did not survive due to the ADRs during hospitalization’ (Line 146-147)

Response: Amendment have been made as suggested.

Elisabetta Poluzzi (Reviewer 2)

The manuscript by Danial et al. deals with the risk of fatal adverse drug reactions (ADRs) in patients with chronic kidney disease (CKD). Authors aimed to develop a risk score to support clinicians in preventing death due to ADRs in this population, by performing a retrospective analysis on a sample of patients admitted to a large hospital in Malaysia. Specific variables impacting on death were identified by different models and appropriate scores were assigned to each of variables. Even the best developed model resulted in a modest performance, nevertheless the Authors stated that it can be clinically useful.
The topic of this study is certainly important by a clinical point of view and the Authors planned a number of methodological steps towards a definition of a performant model.

Response: Thank you so much Dr Elisabetta Poluzzi for acknowledging this study as an important study from the clinical perspective.

However, many limitations should be considered.

Response: The many limitations of this manuscript have been addressed to enhance its readability.

1. I understand that the score aims to predict the risk of death of CKD patients experienced ADRs (not the overall risk of death in CKD patients, nor the overall risk of ADR with fatal outcome). The first aspect that should be clarified is in fact the exact aim and the coherent methodological approach. Authors seem to select patients with ADRs during hospitalization and to assess the risk of death in this specific subpopulation. If this is the case, Authors should make it clearer along the manuscript.

Response: Amended (lines 73-74).

2. The overall risk of in-hospital serious ADRs in patients with CKD would also be a very important aim and it could be addressed with a larger eligible population and a relevant higher power of the analysis. As a matter of fact, only 160 patients were eligible for the present analysis and only 28 did not survive after ADR. The power of the study is very low and the modest performance of the model is probably due to this limitation. The causal relationship between ADRs and death in this population at high risk of death is very difficult to be established, because of the high number of risk factors (CKD and concomitant diseases).

Response: Amended and added in the limitation section (lines 347-351).

3. The type of identified ADRs in eligible patients should be described, in terms of diagnosis and reported drugs, in a Table to be included in the main text.

Response: Eligible patients’ survivability in terms diagnosis of the identified ADRs were thoroughly discussed and published in BMC Pharmacology and Toxicology. 19(1):52. doi: 10.1186/s40360-018-0243-0. Nevertheless, few important findings were added in this manuscript (lines 210-215).
Response: Information on ADRs causative drugs from this study are described and submitted for publication in another journal.

4. The routine ADR reporting process in Malaysia should be better described (lines 85-90), also in terms of annual reporting rate (in-hospital vs. out-of-hospital), as well as in terms of percentage of serious ADRs.

Response: Amended and added (lines 49-60). The lines 85-90 were the methods used in the study for data collection. Identification of ADRs were described in lines 94-107.

5. The paragraph 132-136 should be moved to the results.

Response: Amended. The paragraph 132-136 have been moved to the results section (lines 180-183).

6. The discussion needs an extensive revision, by mainly focusing on ADRs and the relevant possible mechanisms rather than on concomitant diseases.

Response: Amended and added few lines on ADRs (lines 222-230). However, extensive write up on ADRs and its relevant possible mechanisms were not done in this manuscript as the primary focus of this manuscript were more to elaboration on the mortality predictors among the CKD patients. The ADRs and the relevant possible mechanisms were described extensively along with information on ADRs causative drugs from this study and submitted for publication in another journal.

7. English language has to be strongly revised.

Response: Apologies for the many grammatical errors as English is not the Native language in Malaysia. Nevertheless, as to improve readability and flow of our manuscript, we have approached someone whom extensively publishes his articles in international journals to review this manuscript before submission.