PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prognostic models for the clinical management of malaria and its complications: a systematic review
AUTHORS	Njim, Tsi; Tanyitiku, Bayee

VERSION 1 - REVIEW

REVIEWER	Ishag Adam University of Khartoum, Sudan
REVIEW RETURNED	30-Apr-2019

GENERAL COMMENTS	I suggest to mention the STROBE with the reference cited

REVIEWER	Dr Laura Bonnett University of Liverpool, UK
REVIEW RETURNED	20-May-2019

GENERAL COMMENTS	This was a very interesting review of prognostic models for the clinical management of malaria. It was generally very good. I have only a couple of minor comments, primarily that the quality of the studies should be assessed using the PROBAST tool, which is specifically designed for this purpose. For example, it would down-weight studies that have used the Hosmer-Lemeshow method for internal validation as this is no longer considered a valid statistical approach. I appreciate that PROBAST has only recently been published, however. The full reference is: Wolff RF, Moons KG, Riley RD, Whiting PF, Westwood M, Collins GS, et al. PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. Ann Intern Med. 2019;170:51–58. doi: 10.7326/M18-1376. I also have concerns over the discussion which is highly technical and appears to discuss causation rather than factors being predictive of outcome. Other very minor comments are as follows: 1. Add the year that the search was undertaken to the abstract 2. Limiting a search to studies in English is a potential limitation and this should, therefore, be discussed. 3. It is usual practice to check the reference list of relevant systematic reviews to identify additional studies. Was this done within this review? 4. The data extraction should also include the list of prognostic factors contained within each prognostic model.

	5. Validation should be assessed via discrimination and calibration. The manuscript currently only discusses calibration. Is this because included studies did not include calibration or because data on calibration was not extracted from included studies? This should be clarified within the manuscript. 6. Page 6, line 25 - the authors mention "prognosticate". The term is used when discussing the risk of children developing severe anaemia if they were infected with malaria. I believe that this is, therefore, a prediction model rather than a prognostic model and therefore potentially should not be included in the review. Further justification will be required if the study is included. [Note: predictive models predict outcome in people without a condition whilst prognostic models predict outcome in people with a condition] 7. There is a slight problem with the sub-headings in the "models predicting mortality in severe malaria" section - the text does not always match the sub-heading. 8. Rather than saying "the model was not validated" I suggest explicit mention of internal and/or external validation. 9. Ensure all abbreviations are defined the first time they are used e.g. MAP and MPI. 10. Was the 1995 Wilairantana model developed using logistic or Cox regression? 11. Briefly summarise study quality in the Discussion. 12. Include the list of abbreviations in alphabetical order 13. Consider ordering Appendix Table 3a and 3b somehow - possibly by alphabetical order of surname? Also, justify the inclusion of 2 tables; I presume it is due to space constraints?

REVIEWER	Alinune Kabaghe College of Medicine, University of Malawi, Malawi
REVIEW RETURNED	07-Aug-2019

GENERAL COMMENTS	This is a well and clearly written paper addressing research and its direct influence on improving clinical practice. However, the authors only searched one database for the published literature on the subject; there are several other databases which may add to some missing data. I would recommend the authors to consider engaging an information specialist to retrieve the relevant data. Page 6:Hb and AUC should be spelled in full on first mention. Page 6: The level of hemoglobin of 50 g/dl is very high and cannot be regarded as anemia Page 6: which sex, gravidity and season were predictors of anemia? Page 7: worth mentioning the Blantyre coma score 0/5 Page 11: The first paragraph of the discussion is simply a repetition of what is already in the results. Please discuss what is in your findings. Page 11: The second paragraph of the discussion seems misplaced. Consider including that information in your introduction as one of the reasons for conducting this review For the discussion, I would urge the authors to read some guides on how to write a good discussion for a scientific paper.

REVIEWER	Benjamin Jelle Visser Amsterdam University Medical Centre (Amsterdam UMC) Netherlands
REVIEW RETURNED	11-Aug-2019

GENERAL COMMENTS	This papers is a nice overview of the literature. However, I feel that a "clear message" is still missing in this paper. As clinical doctor I would really see easily what I can learn from this paper; in other words, what can I change in daily practise tomorrow when I see a malaria patient? The authors describe several factors that are biological plausible to be an important predictor of severity, and most of the time, also death. I think the literature jusitifies if the authors express their opinions more, and that they provide a table or figure with factors which they think are "strong predictors of mortality of morbidity/complications". If this is one figure, it is easily read and i do not have to screen the whole paper. I am aware that this might be difficult for the authors to do since this is subjective; but otherwise nothing will change. So can the authors recommed which factors are, according to them and the literature, are strong and good factors to asses morbidity and mortality? What can I learn my fellow collegueas about this. And could to authors make also a list with recommendation for future research in prognostic models: which factors, in your opinion, should be definitely addresses? since you are the experts on this subject you probably can provide a valuable list for a phd student on the other side of the world who is now desiging her/his prognostic trial. Than your paper can provide valuable information. Futher more some minor remarks: Page 3 line 20 “this parasitic” is not clear whether they mean vivax or malaria in general. Page 3 line 23: do they have more uptodate numbers? Methods: did the authors register the review in the prospero database? I recommend that more sources are searched: for example besides pubmed/medline:, Embase, The Cochrane Library, Web of Science, BIOSIS Previews, the African Index Medicus, AJOL, and Google Scholar > otherwise you take the risk of missing a few papers… Page 4 line 22: “grey literature” > screening references list is not the recommended method to identify these papers. You should search in other databases too, see comment above. - please mention that you exclude animal models for disease severity - page 5 line 32: so you assessed bias and quality; but how did you handle the results and what did you do with lower quality studies? - factors that predict disease severity: did you see in the studies “clinical judgement from a health professional anywhere?” So in conclusion: your paper would definitely benefit from 1 adding a table or figure with the factors associated with morbidity and mortality, in your subjective opinion and based on the literature 2. provide a list of factors that should definitely be incorporated in future risk predicties studies (this will also increase impact of your review and increase citations rates)

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1

Reviewer Name: Ishag Adam

Institution and Country: University of Khartoum, Sudan

Please state any competing interests or state ‘None declared’: None declared

I suggest to mention the STROBE with the reference cited

Response to reviewer: Thank you for your very kind words on our review. As per the requests of the other reviewers, we have used the PROBAST tool to assess risk of bias and applicability of the models.

Reviewer: 2

Reviewer Name: Dr Laura Bonnett

Institution and Country: University of Liverpool, UK

Please state any competing interests or state ‘None declared’: None declared

This was a very interesting review of prognostic models for the clinical management of malaria. It was generally very good.

Response to reviewer: Thank you for your kind comments.

I have only a couple of minor comments, primarily that the quality of the studies should be assessed using the PROBAST tool, which is specifically designed for this purpose. For example, it would down-weight studies that have used the Hosmer-Lemeshow method for internal validation as this is no longer considered a valid statistical approach. I appreciate that PROBAST has only recently been published, however. The full reference is: Wolff RF, Moons KG, Riley RD, Whiting PF, Westwood M, Collins GS, et al. PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. Ann Intern Med. 2019;170:51–58. doi: 10.7326/M18-1376.

Response to reviewer: Thank you for this suggestion. We have now used this tool to assess risk of bias and applicability of the articles and models used in the review.

I also have concerns over the discussion which is highly technical and appears to discuss causation rather than factors being predictive of outcome.

Response to reviewer: Thank you for this observation. We tried to strike a fine balance by describing how a factor could cause mortality and/or disease severity which may explain its weighting for the prediction of mortality; without sounding too technical. We did this as the article aims to target clinicians to improve clinical practice.

We have made some alterations to the discussion and hopefully this could make an easier read.

Other very minor comments are as follows:

1. Add the year that the search was undertaken to the abstract

Response to reviewer: Thank you. This has been included in the abstract.

2. Limiting a search to studies in English is a potential limitation and this should, therefore, be discussed.

Response to reviewer: This is a very fair comment. We have discussed this as a potential limitation in the paper.

3. It is usual practice to check the reference list of relevant systematic reviews to identify additional studies. Was this done within this review?

Response to reviewer: Indeed, it is usual practice to canvass relevant systematic reviews to identify further studies. We however did not find any reviews published on the use of models to predict clinical outcomes in malaria. We therefore settled on canvassing the reference lists of all the eligible papers in the review to identify similar papers.

4. The data extraction should also include the list of prognostic factors contained within each prognostic model.

Response to reviewer: Thank you for this comment. In the tables that summarize the models included in the review, the 15th column is titled “variables used” and lists the prognostic factors that were included in each model.

5. Validation should be assessed via discrimination and calibration. The manuscript currently only discusses calibration. Is this because included studies did not include calibration or because data on calibration was not extracted from included studies? This should be clarified within the manuscript.

Response to reviewer: Thank you for this comment. We strived to extract both data on the calibration and discrimination of the models where they were used. But as rightly observed, most of the studies provided data only on model calibration or validation was not done at all. We have now clarified this within the manuscript on Page 5 Line 2.

6. Page 6, line 25 - the authors mention "prognosticate". The term is used when discussing the risk of children developing severe anaemia if they were infected with malaria. I believe that this is, therefore, a prediction model rather than a prognostic model and therefore potentially should not be included in the review. Further justification will be required if the study is included. [Note: predictive models predict outcome in people without a condition whilst prognostic models predict outcome in people with a condition]

Response to reviewer: Thank you for this crucial observation. We agree. This study followed up a cohort of newborns until the episode of first severe malaria and anaemia. It should therefore not be included in the review.

Action: This study has been excluded from the review.

7. There is a slight problem with the sub-headings in the "models predicting mortality in severe malaria" section - the text does not always match the sub-heading.

Response to reviewer: Thank you for this observation. The texts and sub-headings have been amended.

8. Rather than saying "the model was not validated" I suggest explicit mention of internal and/or external validation.

Response to reviewer: Thank you for this comment. Explicit mention of internal and/or external validation has been made use of in all instances.

9. Ensure all abbreviations are defined the first time they are used e.g. MAP and MPI.

Response to reviewer: Thank you. All abbreviations have been defined on first use.

10. Was the 1995 Wilairantana model developed using logistic or Cox regression?

Response to reviewer: Wilairantana model in 1995 simply validated the use of the APACHE II model in predicting mortality in adult severe malaria. The original model was produced in 1985 by Knaus et al and clinical judgement and physiologic relationships were used to assign weightings for the factors in the model. We have now made this clear in the manuscript.

11. Briefly summarise study quality in the Discussion.

Response to reviewer: We have summarized the study qualities in the eight of paragraph of the discussion.

12. Include the list of abbreviations in alphabetical order

Response to reviewer: Thank you. This has now been updated.

13. Consider ordering Appendix Table 3a and 3b somehow - possibly by alphabetical order of surname? Also, justify the inclusion of 2 tables; I presume it is due to space constraints?

Response to reviewer: We have now removed these tables as we have used the PROBAST tool for risk of bias assessment.

Reviewer: 3

Reviewer Name: Alinune Kabaghe

Institution and Country: College of Medicine, University of Malawi, Malawi

Please state any competing interests or state ‘None declared’: None Declared

This is a well and clearly written paper addressing research and its direct influence on improving clinical practice.

Response to reviewer: Thank you for your kind comment.

However, the authors only searched one database for the published literature on the subject; there are several other databases which may add to some missing data. I would recommend the authors to consider engaging an information specialist to retrieve the relevant data.

Response to reviewer: Thank you for your suggestion. We have engaged an information specialist and have extended our database search to three databases – Medline, CINAHL and Global Health.

Page 6:Hb and AUC should be spelled in full on first mention.

Response to reviewer: These have been corrected as requested. Thank you.

Page 6: The level of hemoglobin of 50 g/dl is very high and cannot be regarded as anemia

Response to reviewer: Thank you for this comment. As per the observation and request of the above reviewer, this study has been removed from the review.

Page 6: which sex, gravidity and season were predictors of anemia?

Response to reviewer: Thank you for this observation. As per the observation and request of the above reviewer, this study has been removed from the review.

Page 7: worth mentioning the Blantyre coma score 0/5

Response to reviewer: Thank you very much for this correction. It has been implemented as proposed.

Page 11: The first paragraph of the discussion is simply a repetition of what is already in the results. Please discuss what is in your findings.

Response to reviewer: Thank you for your comment. From the template provided by the journal, the first paragraph of the discussion is used to summarize the findings from the results.

Page 11: The second paragraph of the discussion seems misplaced. Consider including that information in your introduction as one of the reasons for conducting this review

Response to reviewer: Thank you for your comment. This paragraph has now been removed from the discussion.

For the discussion, I would urge the authors to read some guides on how to write a good discussion for a scientific paper.

Response to reviewer: Thank you for your recommendation. We have made significant alterations to the discussion.

Reviewer: 4

Reviewer Name: Benjamin Jelle Visser

Institution and Country: Amsterdam University Medical Centre (Amsterdam UMC), Netherlands

Please state any competing interests or state ‘None declared’: none declared

This papers is a nice overview of the literature.

Response to reviewer: Thank you for your kind comments.

However, I feel that a "clear message" is still missing in this paper. As clinical doctor I would really see easily what I can learn from this paper; in other words, what can I change in daily practise tomorrow when I see a malaria patient? The authors describe several factors that are biological plausible to be an important predictor of severity, and most of the time, also death. I think the literature jusitifies if the authors express their opinions more, and that they provide a table or figure with factors which they think are "strong predictors of mortality of morbidity/complications". If this is one figure, it is easily read and i do not have to screen the whole paper. I am aware that this might be difficult for the authors to do since this is subjective; but otherwise nothing will change. So can the authors recommed which factors are, according to them and the literature, are strong and good factors to asses morbidity and mortality? What can I learn my fellow collegueas about this.

And could to authors make also a list with recommendation for future research in prognostic models: which factors, in your opinion, should be definitely addresses? since you are the experts on this subject you probably can provide a valuable list for a phd student on the other side of the world who is now desiging her/his prognostic trial. Than your paper can provide valuable information.

Response to reviewer: Thank you for your kind comments and suggestions to improve our paper. We have now included a list of what we think are imperative factors to be considered by physicians when faced with a patient with malaria infection in the discussion. “Figure 2” has also been used to summarize these factors.

Futher more some minor remarks:

Page 3 line 20 “this parasitic” is not clear whether they mean vivax or malaria in general.

Response to reviewer: Thank you for this observation. We meant to say malaria infection in general.

Action: We have corrected the sentence to now read: “Malaria infection can result in severe disease…”

Page 3 line 23: do they have more uptodate numbers?

Response to reviewer: Thank you for your suggestion. We have used the latest WHO malaria figures of 2019 which gives the number of people who died globally from the disease in 2017.

Action: The sentence now reads: “In about 108 countries where the transmission of the disease still occurs, an estimated 435,000 people died in 2017”.

Methods: did the authors register the review in the prospero database?

Response to reviewer: The review was registered in the prospero database. The review number - CRD42019130673, has now been included in the paper.

I recommend that more sources are searched: for example besides pubmed/medline:, Embase, The Cochrane Library, Web of Science, BIOSIS Previews, the African Index Medicus, AJOL, and Google Scholar

> otherwise you take the risk of missing a few papers…

Response to review: Thank you for your suggestion. We have now increased the number of databases searched to three databases – Medline, CINAHL and Global Health.

Page 4 line 22: “grey literature” > screening references list is not the recommended method to identify these papers. You should search in other databases too, see comment above.

Response to reviewer: This is a fair comment. We have removed the phrase “grey literature” and simply stated that we canvassed references for other papers. We have also increased the number of databases searched.

- please mention that you exclude animal models for disease severity

Response to reviewer: Thank you for the suggestion. We have included this in the paper.

- page 5 line 32: so you assessed bias and quality; but how did you handle the results and what did you do with lower quality studies?

Response to reviewer: Thank you for your comment. As per the request of one of the reviewers, we have now used the PROBAST tool to assess bias and quality. After using this tool, we determined that all of the articles had a high risk of bias due to lack of use of adequate statistical methods for validation or the absence of any internal validation. We have therefore recommended caution in the interpretation of these results.

- factors that predict disease severity: did you see in the studies “clinical judgement from a health professional anywhere?”

Response to reviewer: We did not see any article that used clinical judgement for the prediction of disease severity. However, the original APACHE model produced in 1985 by Knaus et al used clinical judgement in assigning weightings for their variables. This has been stated in the manuscript.

So in conclusion: your paper would definitely benefit from

1 adding a table or figure with the factors associated with morbidity and mortality, in your subjective opinion and based on the literature

Response to reviewer: We have added “Figure 2” which summarizes the various factors associated with disease severity and mortality in malaria.

2. provide a list of factors that should definitely be incorporated in future risk predicties studies (this will also increase impact of your review and increase citations rates)

Response to reviewer: We have listed the factors which we think need to be considered in future predictive studies in the discussion.

VERSION 2 – REVIEW

REVIEWER	Dr Laura Bonnett University of Liverpool, UK
REVIEW RETURNED	23-Sep-2019

GENERAL COMMENTS	Dear authors, Thank you for responding so well to all the comments from the reviewers. I believe that this has greatly improved the review. I have one outstanding query. This is new, and as a result of you updating your searches. Currently, there is a problem with the number of included studies in the abstract, results, discussion and PRISMA flow diagram. You say 24 studies and models were included. However, in the abstract 3+15+3+4=25. In the PRISMA diagram, you have 59-9-2-23=25 rather than 24. In the discussion, the total is 27 and in the results the total is unclear. Please define + and - in appendix 3 too. Otherwise, well done and thank you for undertaking this interesting review.

REVIEWER	Alinune Kabaghe College of Medicine, University of Malawi
REVIEW RETURNED	13-Oct-2019

GENERAL COMMENTS	Well written.

REVIEWER	BJ Visser Amsterdam UMC, location AMC Netherlands
REVIEW RETURNED	29-Oct-2019

GENERAL COMMENTS	The authors addressed all my comments and together with the comments of the other reviewers the paper has improved. I am also happy that they included a figure (figure 2) to see at once which factors (are mainly) described leading to complicatons, severity, or mortality. I think the figure is fine as it is, but can be improved a little bit. For example, hypoglycemia is now a "seperate" risk factor, but it also gives more neurologica dysfunction. However this figure can be quite difficult to make, since biological mechanisms are not always clear. However, I would prefer a human body in the background, with arrows and "risk factors's" so that it is more attractive as an illustration. For example (https://commons.wikimedia.org/wiki/File:Symptoms_of_influenza.svg) last comment is that i would like to see a more specific next research directions, or a table with "research gaps" > how do they see the future? is artifiical intelligence something that can be used in the future to predict malaria severity? and is this feasible in most settings or not a possiblity in near future in low resource settings?

VERSION 2 – AUTHOR RESPONSE

RESPONSES TO REVIEWERS' COMMENTS

Reviewer Name: Dr Laura Bonnett

Dear authors,

Thank you for responding so well to all the comments from the reviewers. I believe that this has greatly improved the review.

I have one outstanding query. This is new, and as a result of you updating your searches. Currently, there is a problem with the number of included studies in the abstract, results, discussion and PRISMA flow diagram. You say 24 studies and models were included. However, in the abstract 3+15+3+4=25. In the PRISMA diagram, you have 59-9-2-23=25 rather than 24. In the discussion, the total is 27 and in the results the total is unclear.

Response to reviewer: Thank you for this observation. We have clarified in the manuscript and flow chart. There were 24 articles in total that met our criteria. These articles reported on 27 models. This is because one of the articles reported on 3 models, another reported two models while the rest reported one model each.

Please define + and - in appendix 3 too.

Response to reviewer: Thank you. These signs have been defined in the appendices.

Otherwise, well done and thank you for undertaking this interesting review.

Response to reviewer: Thank you very much for your comments which greatly improved the review.

Reviewer: 3

Reviewer Name: Alinune Kabaghe

Well written.

Response to reviewer: Thank you very much for your comments which have improved the manuscript.

Reviewer: 4

Reviewer Name: BJ Visser

The authors addressed all my comments and together with the comments of the other reviewers the paper has improved.

Response to reviewer: Thank you very much for the suggestions you made to improve our paper.

I am also happy that they included a figure (figure 2) to see at once which factors (are mainly) described leading to complicatons, severity, or mortality. I think the figure is fine as it is, but can be improved a little bit. For example, hypoglycemia is now a "seperate" risk factor, but it also gives more neurologica dysfunction. However this figure can be quite difficult to make, since biological mechanisms are not always clear. However, I would prefer a human body in the background, with arrows and "risk factors's" so that it is more attractive as an illustration. For example (https://commons.wikimedia.org/wiki/File:Symptoms_of_influenza.svg)

Response to reviewer: Thank you very much for this suggestion. It has indeed made the illustration clearer.

last comment is that i would like to see a more specific next research directions, or a table with "research gaps" > how do they see the future? is artifiical intelligence something that can be used in the future to predict malaria severity? and is this feasible in most settings or not a possiblity in near future in low resource settings?

Response to reviewer: Thank you for this comment. We have included table 5 which summarizes our research findings, addresses the research gaps and gives potential future research possibilities. We think artificial intelligence is definitely the next step after robust models have been designed. These models could most certainly be incorporated into applications that predict the risk of severity after patient data has been inputted and the suggestion of management modalities.