PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A retrospective study of platelet-to-lymphocyte ratio as a prognostic predictor of mortality for sepsis: interaction effect with disease severity
AUTHORS	Shen, Yanfei; Huang, Xinmei; Zhang, Weimin

VERSION 1 – REVIEW

REVIEWER	Mustafa Oylumlu Dicle University Faculty of Medicine, Department of Cardiology, Dİyarbakir/Turkey
REVIEW RETURNED	21-Mar-2018

GENERAL COMMENTS	Well designed and organised manuscript. Patient size is adequate, materil and method is well described, results are shown in detail. Discussion section is well discussed.

REVIEWER	Emine Gazi Canakkale Onsekiz Mart University, Turkey
REVIEW RETURNED	28-Mar-2018

GENERAL COMMENTS	I have read the manuscript entitled "Platelet to lymphocyte ratio as a prognostic predictor of mortality for sepsis: Interaction effect with disease severity. A retrospective study" with a great interest. Although methods and results well described, it is need to explantation some points 1. Is this study population including patients with malignities? It is well known some cancer types affect to hematological parameters especially platelet counts. If cancer patients enrolled in this study, this variable should be discussed.

REVIEWER	Diana Tilevik University of Skövde, Sweden
REVIEW RETURNED	28-Mar-2018

GENERAL COMMENTS	This paper describes a retrospective study by Yanfei et al. The aim of the study is to investigate the prognostic value of platelet-to-lymphocyte ratio for sepsis. My major concern about this paper is the interpretation of the results. As an OR of 1.00 indicates that the risk is comparable in the two groups, I would say that an OR of 1.002 is not impressing, the effect size is very, very small. The statistical significance as indicated by the 95% CI is just a result of a very large sample size, n=5,537 sepsis patients. Another concern is that the authors use predictive sometimes and prognostic sometimes. However,

	these two terms shouldn´t be mixed up. A prognostic biomarker provides information about the patients overall outcome, regardless of therapy, whilst a predictive biomarker gives information about the effect of a therapeutic intervention. There is nothing called insignificant – should be non-significant. Research question It is stated that the objective is to investigate the predictive value of PLR for sepsis. This is not correct as you investigate the prognostic value of PLR for sepsis (see my previous comment regarding predictive and prognostic markers). Ethics The approval number for the ethical permission by the ethical board is not provided. Materials and method • On page 6, the authors say that the baseline values for SCr, etc. were missing for 20% of the cases and replaced with imputed values. However, it is not recommended to impute missing values if it is more than 15% for a variable as it will bias the data. • Furthermore, variables with less than 5% of missing values were replaced by the mean values. However, you should only use mean values for normally distributed data. Otherwise it is better to use the median. • How about variables with missing values between 5% and 20%? How were these handled? • Motivation for including variables having a p-value<0.20 in the univariate analyses, in the multivariate logistic regression? • How did the authors handle the detected multicollinearity?

REVIEWER	JESUNG YOU Yonsei University College of Medicine
REVIEW RETURNED	03-Apr-2018

GENERAL COMMENTS	This study demonstrated that High PLRs at admission were associated with an increased risk of severity about sepsis. Firstly, this study had large samples relatively. I think that PLR also simple and impressive marker in sepsis. It is worth to consider as meaningful article. However, there are some flaws 1. Author revealed univariate results in revision. 2. I can not agree with variables in multivariable analysis. (How to select variables in multivariable analysis) Author have to propose appropriate variables according to univariable analysis and standard (p <0.05?, p<0.1?) 3. I also can not agree with your opinion. Did OR 1.0002 have clinically significance? clarify this point - In the logistic model with linear spline function, a PLR > 200 was significantly (odds ratio [OR], 1.0002; 95% confidence interval [CI], 1.0001 – 1.0004) associated with mortalit0y; 4. Clarify IRB review- MIT? only using database? How did you deal with information about patients - Did not neew to review this study by hospital IRB ? I know that the study was performed in China.

VERSION 1 – AUTHOR RESPONSE

11-May-2018

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Mustafa Oylumlu

Institution and Country: Dicle University Faculty of Medicine, Department of Cardiology, Dİyarbakir/Turkey

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

Please leave your comments for the authors below
Well designed and organised manuscript.
Patient size is adequate, materil and method is well described, results are shown in detail. Discussion section is well discussed.

Answer: Thank you for your comments!

Reviewer: 2
Reviewer Name: Emine Gazi

Institution and Country: Canakkale Onsekiz Mart University, Turkey

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

Please leave your comments for the authors below
I have read the manuscript entitled "Platelet to lymphocyte ratio as a prognostic predictor of mortality for sepsis: Interaction effect with disease severity. A retrospective study" with a great interest.
Although methods and results well described, it is need to explantation some points
1. Is this study population including patients with malignities? It is well known some cancer types affect to hematological parameters especially platelet counts. If cancer patients enrolled in this study, this variable should be discussed.

Answer: Thank you for your advice. We agree with your opinion that the platelet count was affected by many cofounders, such as types of malignities, immunological factors, and types of drugs. However, due to the retrospective nature of our study, these situations cannot be identified with the data available. For example, in a patient with cancer, information about whether the tumor stabilized or was removed by surgery, or whether the patients underwent chemotherapy, is lacking. We admit this is a limitation of our study and this is now discussed in the limitation section now. Thank you for your great suggestion! (Page 14, Paragraph 2)

Reviewer: 3
Reviewer Name: Diana Tilevik

Institution and Country: University of Skövde, Sweden

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

This paper describes a retrospective study by Yanfei et al. The aim of the study is to investigate the prognostic value of platelet-to-lymphocyte ratio for sepsis.

My major concern about this paper is the interpretation of the results. As an OR of 1.00 indicates that the risk is comparable in the two groups, I would say that an OR of 1.002 is not impressing, the effect size is very, very small. The statistical significance as indicated by the 95% CI is just a result of a very large sample size, n=5,537 sepsis patients.

Answer: Thank you for your comments. Your concern is understandable. However, we would like to explain this from three aspects. First, the small OR is based on the wide range of PLR values. A knot was detected in the association between PLR and mortality. Considering that translating the PLR into a categorical variable would weaken the statistical power to detect a true association, a linear spline function was initially used in the multivariate logistic regression, using PLR as a continuous variable. The resulting OR, although very small at 1.0002, only represented the change of odds per PLR unit increase. As the range of PLR values is relatively wide (5% - 95% value range: 49.2–909.1), we think the result is explicable. For example, the OR will become 1.02 if we take 100 units of PLR as one unit in logistic models. Second, as the prognosis of ICU patients was affected by many confounding factors, it is reasonable that a single index has a relative small OR. A recent study (Oh et al., PMID: 27504801) investigated the prognostic value of mean platelet volume/platelet count (MPV/PLT) and platelet distribution width/platelet count (PDW/PLT) of mortality in sepsis, and ORs were also reported. For a better understanding, we made some comparisons in a table below. In all comparisons, when we narrowed the interquartile range of PLR to the reported interquartile range of MPV/PLT or PDW/PLT, the crude ORs become comparable. Additionally, white blood cell (WBC) and platelet count are important biochemical indices for sepsis, and are also commonly reported as categorical variables in regression models. In the table below, we also presented the ORs of WBC and platelet count of mortality, using them as continuous variables. We found that the ORs of WBC and PLT are comparable to the OR of PLR in our study, considering the interquartile range of respective variables.

Variables	**Crude OR (95% CI)**	**Median (IQR)**
MPV/PLT (Oh et al.’s study, Table 2)	1.043 (1.022 – 1.063)	4.39 (3.30 – 7.81)
PLR/50		Overall: 4.3 (2.5 – 7.4)
≤ 4	0.869 (0.82 – 0.92)	
> 4	1.014 (1.006 – 1.022)	
PDW/PLT (Oh et al.’s study, Table 2)	1.004 (1.001 – 1.007)	28.4 (20.9 – 53.0)
PLR/8		Overall: 27 (15.6 – 46.2)
≤ 25	0.977 (0.96 – 0.98)	
> 25	1.002 (1.001 – 1.003)	

White blood cell count	1.013 (1.007 – 1.019)	12.5 (8.6 – 17.5)
Platelet		Overall: 205 (134 – 296)
< 200	0.993 (0.991 – 0.994)	
> 200	1.0003 (0.9997–1.0009)	

Comparisons of ORs with different interquartile ranges.

Finally, for better interpretation, PLR was further divided into three levels in our study and the ORs are more significant. In disease severity scoring tools, such as APPACHE II and SOFA, all of the important indexes including WBC and PLT are used as categorized variables instead of continuous variables. We hope that our findings will add some useful information to the prognostic tools of sepsis in future studies.

Another concern is that the authors use predictive sometimes and prognostic sometimes. However, these two terms shouldn´t be mixed up. A prognostic biomarker provides information about the patients overall outcome, regardless of therapy, whilst a predictive biomarker gives information about the effect of a therapeutic intervention.

Answer: Thank you for the detailed explanation. We now understand the difference between prognostic and predictive values and have revised this throughout the manuscript.

There is nothing called insignificant – should be non-significant.

Answer: Thank you for this comment. This has been thoroughly revised in the manuscript.

Research question
It is stated that the objective is to investigate the predictive value of PLR for sepsis. This is not correct as you investigate the prognostic value of PLR for sepsis (see my previous comment regarding predictive and prognostic markers).

Answer: This has been revised. Thank you.

Ethics
The approval number for the ethical permission by the ethical board is not provided.

Answer: Thank you for your advice. The ethical approval statement is now added after the conclusion section as follow: The use of this database was approved by the review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. All patient information in the database has been de-identified for privacy protection and the need for informed consent was waived.

Materials and method
On page 6, the authors say that the baseline values for SCr, etc. were missing for 20% of the cases and replaced with imputed values. However, it is not recommended to impute missing values if it is more than 15% for a variable as it will bias the data.

Answer: We agree with your opinion. Due to the large percentage of missing values of SCr, multiple imputation method is barely suitable if this variable is included in the regression model. However, in the current study, baseline SCr was used in the definition of AKI, thus, multiple imputation is not appropriate. On the other hand, in order to minimize the potential bias, we inputted the missing value using a reported estimation equation, with a reported median absolute error of 0.1–0.2 mg/dl. However, as the baseline SCr was only used in the subgroup analysis, we believe that the bias will be relatively small.

• Furthermore, variables with less than 5% of missing values were replaced by the mean values. However, you should only use mean values for normally distributed data. Otherwise it is better to use the median.

Answer: Thank you for your advice. You are right. We did input the missing value with the median of non-normal distribution parameters, such as the SOFA score. However, we did not state this clearly in the manuscript. The description of this method has been revised.

• How about variables with missing values between 5% and 20%? How were these handled?

Answer: Missing values are common in the MIMIC III database, as it comprises more than 58,000 admissions. However, most of them are less than 5%. We noticed that the percentage of missing value of serum lactate and albumin is 12.9% and 26.3%, respectively. Thus, albumin was excluded from our analysis. Additionally, the missing value of serum lactate was not inputted, and the number of missing values was indicated in the crude comparison in Table 1. (Maximum serum lactate 4.1 ± 3.8 (n=1536) 3.4 ± 3.1 (n=1174) 3.1 ± 3.0 (n=2112)).

• Motivation for including variables having a p-value<0.20 in the univariate analyses, in the multivariate logistic regression?

Answer: Although the proper p-value for the selection of confounders remains controversial, p-value of 0.02 is a conventional level and is supported by literature (PMID: 2910056) and was also adopted in other studies (PMID: 23089680)

• How did the authors handle the detected multicollinearity?

Answer: Multi-collinearity was tested using the variance inflation factor (VIF) in this study. The VIF was reported for the logistic model and no obvious multicollinearity was detected.

Thank you for your comments!

Reviewer: 4
Reviewer Name: JESUNG YOU

Institution and Country: Yonsei University College of Medicine

Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below
This study demonstrated that High PLRs at admission were associated with an increased risk of severity about sepsis. Firstly, this study had large samples relatively.
I think that PLR also simple and impressive marker in sepsis.
It is worth to consider as meaningful article.
However, there are some flaws
1. Author revealed univariate results in revision.

Answer: Thank you for your advice. Then univariate results are now added in the supplementary file (Table S1).

2. I can not agree with variables in multivariable analysis. (How to select variables in multivariable analysis). Author have to propose appropriate variables according to univariable analysis and standard (p <0.05?, p<0.1?)

Answer: Thank you for your advice. The selection criteria of confounders are described in the statistical section, as follows (Page 7 Paragraph 2): Variables including demographic characteristics, infection sites, disease severity score, and laboratory measures potentially associated with mortality, or those that had a p value < 0.20 in the univariate analyses were initially included in the multivariate logistic regression analyses. P-value of 0.02 is a conventional level and is supported by literature (PMID: 2910056, PMID: 23089680). A stepwise backward elimination method with a significance level of 0.05 was used to build the final model. However, according to our experience (PMID: 28494815), admitted ICU type is an important confounder of mortality (factors such as intensive care and therapeutic regimens may be different in cases admitted to the different ICUs). Thus, the admitted ICU type was also included in the final model despite p-value >0.05.

3. I also can not agree with your opinion.
Did OR 1.0002 have clinically significance? clarify this point
- In the logistic model with linear spline function, a PLR > 200 was significantly (odds ratio [OR], 1.0002; 95% confidence interval [CI], 1.0001 – 1.0004) associated with mortality;

Answer: Thank you for your comments. Your concern is understandable. However, we would like to explain this from three aspects. First, the small OR is based on the wide range of PLR values. A knot was detected in the association between PLR and mortality. Considering that translating the PLR into a categorical variable would weaken the statistical power to detect a true association, a linear spline function was initially used in the multivariate logistic regression, using PLR as a continuous variable. The resulting OR, although very small at 1.0002, only represented the change of odds per PLR unit increase. As the range of PLR values is relatively wide (95% value range: 49.2–909.1), we think the result is explicable. For example, the OR will become 1.02 if we take 100 units of PLR as one unit in logistic models. Second, as the prognosis of ICU patients was affected by many confounding factors, it is reasonable that a single index has a relative small OR. A recent study (Oh et al., PMID: 27504801) investigated the prognostic value of mean platelet volume/platelet count (MPV/PLT) and

platelet distribution width/platelet count (PDW/PLT) of mortality in sepsis, and ORs were also reported. For a better understanding, we made some comparisons in a table below. In all comparisons, when we narrowed the interquartile range of PLR to the reported interquartile range of MPV/PLT or PDW/PLT, the crude ORs become comparable. Additionally, white blood cell (WBC) and platelet count are important biochemical indices for sepsis, and are also commonly reported as categorical variables in regression models. In the table below, we also presented the ORs of WBC and platelet count of mortality, using them as continuous variables. We found that the ORs of WBC and PLT are comparable to the OR of PLR in our study, considering the interquartile range of respective variables.

Variables	**Crude OR (95% CI)**	**Median (IQR)**
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< 200	0.993 (0.991 – 0.994)	
> 200	1.0003 (0.9997–1.0009)	

Comparisons of ORs with different interquartile ranges.

Finally, for better interpretation, PLR was further divided into three levels in our study and the ORs are more significant. In disease severity scoring tools, such as APPACHE II and SOFA, all of the important indexes including WBC and PLT are used as categorized variables instead of continuous variables. We hope that our findings will add some useful information to the prognostic tools of sepsis in future studies.

4. Clarify IRB review- MIT? only using database?
How did you deal with information about patients - Did not neew to review this study by hospital IRB ?
I know that the study was performed in China.

Answer: MIMIC III is an online open-access database. Use of the database for this study was approved by the review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. All patient information in the database was de-identified for privacy protection, and the need for informed consent was waived. This database requests all users to cite this project data, code, or algorithms are used from database. Author Y Shen has obtained access to this database (certification number: 1564657). The ethical approval statement has been added after the conclusion section in the manuscript (Page 15 last paragraph).

VERSION 2 – REVIEW

REVIEWER	Emine Gazi Çanakkale Onsekiz Mart University, Turkey
REVIEW RETURNED	09-Jun-2018

GENERAL COMMENTS	The manuscript is acceptable for publication.

REVIEWER	Diana Tilevik Systems Biology Research Centre, School of Bioscience, University of Skövde
REVIEW RETURNED	05-Jun-2018

GENERAL COMMENTS	The manuscript has been improved, but many of my previous concerns have not been addressed in the revised version. In addition, there seems to be modifications done which are not marked in the manuscript (e.g., parts in the Materials and Methods). Still, my major concern about this paper is the interpretation of the results. Although the authors have provided a motivation, I still do not agree with them. As an OR of 1.00 indicates that the risk is comparable in the two groups, I still would say that an OR of 1.002 is not impressing, the effect size is very, very small. The statistical significance as indicated by the 95% CI is just a result of a very large sample size, n=5,537 sepsis patients. Thus, the authors must be very careful in their interpretation of the results and show that they are aware of this in the manuscript. Ethics The approval number for the ethical permission by the ethical board is still not provided. Materials and method • In the previous version, the authors stated on page 6 that the baseline values for SCr, etc. were missing for 20% of the cases and replaced with imputed values. The authors now say that all variables with more than 20% of missing values (both lactate and albumin) were excluded from the analysis. However, the authors write in their response that the percentage of missing values for serum lactate was 12.9% and for albumin 26.3%, and only albumin was removed. Please clarify in the manuscript how you did handle the missing data of serum lactate. • Did all other variables except for serum lactate and albumin, had a percentage of missing values below 5%? If so, please clarify this in the manuscript (concerning my previous comment about how you did handle variables with missing values between 5% and 20%). I think it is important to also tell the readers this.

	• The following sentence, on page 7: “For non-normal distribution variables with less than 5% of missing values, such as age and fluid balance, we replaced the missing values with the mean values, and for non-normal distribution parameters, missing values were replaced by the respective median, instead of using the multiple imputation technique.” is confusing and incorrect. Please correct it. • In the manuscript the authors state that they have used p-value<0.20 to determine which variables to be included in the multivariate logistic regression. However, in the authors' reply you write a p-value of 0.02. Which p-value should it be? Please also include the mentioned references in the manuscript as support for your choice of p-value. • You say that you have tested for multicollinearity, but you haven’t reported the VIF for the logistic model. Please report the VIF in the Results.

REVIEWER	JESUNG YOU YONSEI UNIVERSITY COLLEGE OF MEDICINE
REVIEW RETURNED	01-Jun-2018

GENERAL COMMENTS	Thank you for your response in detail. It is worthy to publish this article.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 4

Reviewer Name: JESUNG YOU

Institution and Country: YONSEI UNIVERSITY COLLEGE OF MEDICINE

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

Please leave your comments for the authors below

Thank you for your response in detail.

It is worthy to publish this article.

Answer: Thanks for your suggestions on making changes to our manuscript. We have addressed these in the revised manuscript.

Reviewer: 2

Reviewer Name: Emine Gazi

Institution and Country: Çanakkale Onsekiz Mart University, Turkey

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

Please leave your comments for the authors below

The manuscript is acceptable for publication.

Answer: Thanks for your suggestions on making changes to our manuscript we have addressed these in the revised manuscript.

Reviewer: 3

Reviewer Name: Diana Tilevik

(The comments of this review is not positive, please give us some advice. Thanks.)

Institution and Country: Systems Biology Research Centre, School of Bioscience, University of Skövde

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

Please leave your comments for the authors below

The manuscript has been improved, but many of my previous concerns have not been addressed in the revised version. In addition, there seems to be modifications done which are not marked in the manuscript (e.g., parts in the Materials and Methods).

Answer: Thank you for your comments. We have carefully re-reviewed all your previous suggestions, and all your concerns have been addressed point by point in the responses below. All the modifications are now highlighted in the manuscript (Yellow: modification highlighted in the first version; Gray: modifications that should have been highlighted in the first version; Green: modifications made in the current revised manuscript).

Still, my major concern about this paper is the interpretation of the results. Although the authors have provided a motivation, I still do not agree with them. As an OR of 1.00 indicates that the risk is comparable in the two groups, I still would say that an OR of 1.002 is not impressing, the effect size is very, very small. The statistical significance as indicated by the 95% CI is just a result of a very large sample size, n=5,537 sepsis patients. Thus, the authors must be very careful in their interpretation of the results and show that they are aware of this in the manuscript.

Answer: We understand your concerns; this small OR is still based on the wide range of the PLR value. We have addressed your concerns in the limitation paragraph (Page 15, paragraph 1). On the other hand, as PLR was reported a novel inflammatory index, our study fills the gap by providing a better understanding of the prognostic value of PLR in sepsis. We hope we have satisfactorily addressed your concern.

Ethics

The approval number for the ethical permission by the ethical board is still not provided.

Answer: We apologize for not adding this information in the first round of revisions. All the data presented in this study were extracted from an online database named “MIMIC III”, which was approved by the review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. Thus, requirement for individual patient consent was waived because the study did not impact clinical care and all protected health information was de-identified. This was also reported in previous studies (PMID: 23385106, 25466337). The detailed description of ethical approval has been added to Page 16, Paragraph 3.

Materials and method

In the previous version, the authors stated on page 6 that the baseline values for SCr, etc. were missing for 20% of the cases and replaced with imputed values. The authors now say that all variables with more than 20% of missing values (both lactate and albumin) were excluded from the analysis. However, the authors write in their response that the percentage of missing values for serum lactate was 12.9% and for albumin 26.3%, and only albumin was removed. Please clarify in the manuscript how you did handle the missing data of serum lactate.

Answer: We apologize for this confusion. The percentage of missing values of baseline SCr, lactate and albumin was 20.3%, 12.9% and 26.3%, respectively. The baseline SCr was used in the definition of AKI in this study. As AKI was not the primary outcome, we used a reported estimation equation (reported median absolute error was 0.1–0.2 mg/dl) to calculate the missing values (The description has been revised in Page 6, Paragraph 3). As the AKI was only used in the subgroup analysis, the main conclusions of adjusted regression analysis would not be affected. For maximum SCr during ICU stay, less than 5% of the cases were missing and was replaced with the mean value as presented in Table 1. As the reviewer indicated, the statement that “Variables with more than 20% of missing values were excluded from our analysis; these included serum albumin and lactate” is confusing. It is now revised in the manuscript (Page 7, Paragraph 2). Actually, in this statement, we mean that both serum lactate and albumin were excluded from the multi-variable regression analysis due to the high proportion of missing values. For serum lactate, 12.9% of the included cases were missing and the crude comparison within three PLR levels is presented in Table 1 both in the first and the current version of the manuscript. The missing value of serum lactate was not filled in this study. The serum albumin was completely excluded from this study (including baseline characteristic comparison and regression analysis). The description has now been revised as follows: The percentage of missing values of serum lactate and albumin was 12.9% and 26.3%, respectively. For serum lactate, the crude comparison within three PLR levels is presented in Table 1, but was not included in the logistic models. The serum albumin was completely excluded from this study (Page 7, Paragraph 2).

Did all other variables except for serum lactate and albumin, had a percentage of missing values below 5%? If so, please clarify this in the manuscript (concerning my previous comment about how you did handle variables with missing values between 5% and 20%). I think it is important to also tell the readers this.

Answer: Yes, the percentage of other variables included in this study was less than 5%, and was replaced by mean or median values. This issue has been addressed in the revised manuscript (Page 7 Paragraph 2).

The following sentence, on page 7: “For non-normal distribution variables with less than 5% of missing values, such as age and fluid balance, we replaced the missing values with the mean values, and for non-normal distribution parameters, missing values were replaced by the respective median, instead of using the multiple imputation technique.” is confusing and incorrect. Please correct it.

Answer: Thank you for your comment. This description has now been revised (Page 7, Paragraph 2).

In the manuscript the authors state that they have used p-value<0.20 to determine which variables to be included in the multivariate logistic regression. However, in the authors' reply you write a p-value of 0.02. Which p-value should it be? Please also include the mentioned references in the manuscript as support for your choice of p-value.

Answer: Sorry for this error. The p value was 0.20 and the references have been cited in the manuscript (Page 8, Paragraph 1). Thanks for your advice.

You say that you have tested for multicollinearity, but you haven’t reported the VIF for the logistic model. Please report the VIF in the Results.

Answer: Thank you for your suggestion. The VIF has been added as a note to Table 3 and now described in the results (Page 9, Paragraph 2). In Table 3, the VIF is 1.87, 1.85, 1.98 and 2.53 in model 1, model 2, model 3 and model 4, respectively.

VERSION 3 – REVIEW

REVIEWER	Diana Tilevik Systems Biology Research Centre, School of Bioscience, University of Skövde, Sweden
REVIEW RETURNED	31-Aug-2018

GENERAL COMMENTS	Thanks for your detailed response. The manuscript is acceptable for publication.