PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Correlation between perioperative parecoxib use and postoperative acute kidney injury in patients undergoing non-cardiac surgery: A retrospective cohort analysis
AUTHORS	Tang, Yong-Zhong; Zeng, Pingping; Liao, Yan; Qin, Zheng; Zhang, Hao; Li, Bo; Ouyang, Wen; li, dan

VERSION 1 – REVIEW

REVIEWER	Hatem Ali University Hospitals Birmingham NHS Foundation Trust
REVIEW RETURNED	03-Mar-2021

GENERAL COMMENTS	Dear Authors, Thank you very much for the hard work in this manuscript. The authors discussed an important topic which is :Drugs that can prevent or reduce incidence of AKI after non-cardiac surgery. The results are very interesting results; they found that Pericoxib can have protective effect against post-operative AKI. The following are major points that need to be addressed in the manuscript: Abstract: 1-The aim of the study is not clear in the abstract. It needs to be clear and easily identified. This is not the case 2-In the methodology, you wrote that you did logistic regression. However, in the results section, you are talking about incidence !. The results section should reflect the methodology. You need to talk about the results of your logistic regression, not the incidence Introduction: The introduction is generally well written. Some Typos that need to be corrected. I would suggest to write more about how NSAIDs can cause AKI as this is an important point in your debate. Methodology: 1-What was the indication of giving Pericoxib? Was it based on the anaesthesia doctor choice? 2-Why the control group didn't receive Pericoxib? Was it a doctor or patient preference? 3-Did the control group receive any other NSAIDs ? like Ibuprofen or Naproxen? How many patients receive these medications? These might be a cause that these patients had a higher incidence of AKI? 4- The above points can cause a confounding by indication, which is a major limitation in the study. 5-Thank you for doing multiple imputation for missing data. However, you need to describe more about the details of multiple imputation. What are the variables you made multiple imputations

	for? And what are the co-variates used for each imputed variable? You need to write more details about this 6-You need to describe more about your sensitivity /subgroup analysis in the methodology section. What type of sensitivity analysis did you do? Why did you choose these subgroups? What analysis have you done? 7-I appreciate in the results section, you did some sensitivity /subgroup analysis about non-smoker, eGFR less than 90….Thank you for that As a Nephrologist, every one working in the Nephrology field knows that the main reason for post-operative AKI is blood loss and hypotension. I appreciate these are variables you have adjusted for in your logistic regression, however, I would be very interested to know the effect of Percoxib on a subgroup of patients that had intra-operative hypotension/ significant blood loss alone, and another subgroup, among those who didn't have hypotension/significant blood loss. This would make more sense to me and would be more important results as a nephrologist. If the Percoxib showed a protective effect in these subgroups, and the control group, didn't receive any other NSAIDs, then I might believe your results. And this will add more strength to it. 8- Thanks for using the KDIGO as a guide to define AKI. I would like to point out that , from the renal point of view, Nephrologists would be much more interested in AKI stage 2 and AKI stage 3. I would suggest to do a sensitivity analysis having your outcome of measurement as AKI3 and see if Pericoxib will reduce this or not? Results: 1-In figure 1, is it the number of excluded patients? It is not clear on the figure what are these numbers. You need to write it down. 2-You need to write down a table summary for the type of surgical operations done and number of patients, if possible. 3- It is obvious from table 1 that the AKI patients had significantly higher percentage of intra-operative hypotension and significant blood loss (>1000ml). For any nephrologist, this would be the main and very obvious cause of AKI. Can you please explain your thoughts how Pericoxib can be protective in patients with significant blood loss and intra-operative hypotension? Definitely , you need to do subgroup analysis among these patients. I would be really interested to see your results in these subgroups ! 4-Table 1 is too big, can go to supplementary data. 5-I just don't understand table 5 or your sensitivity analysis! It is not clear in the methodology or in the results. Please clarify 6-I slightly disagree with your classification for AKI rank. You need to separate AKI 2 from AKI 3 (as per KDIGO guidelines) Discussion: 1-The limitation part is limited. Please use the comments above to expand in your limitations. 2-You need to write down the names of the studies you are discsussing , perhaps use the first author name, rather than saying : a study !

REVIEWER	O Goren Tel Aviv Sourasky Medical Center
REVIEW RETURNED	15-Mar-2021

GENERAL COMMENTS	The authors have conducted an interesting single-center cohort retrospective study aimed at the possible correlation between the intraoperative administration of COX 2 selective parecoxib and

	perioperative AKI. This large study has interesting results and sound methodology. I have a few questions and comments. Why did the authors include ASA 4 patients in the study? These patients are high-risk patients, and I think that many of their surgeries are emergent. Many studies refrain from using ASA 4 patients. What were the author's considerations? Why did the authors exclude any use of surgeries with the use of local anesthetics? Moreover, the authors mention that a certain percentage of the patients were operated not under general anesthesia. If no local anesthetics were used, how were the non-general anesthesia patients operated on? In row 105, the authors mention that the preoperative Cr was defined as the lowest level at preoperative day 7. Can the authors clarify this sentence? Were all the patients hospitalized more than seven days before the surgery? If not – from where were the Cr levels obtained? How was baseline CKD defined? From medical records or calculated from the Cr, BMI and gender? In my opinion, table 1 is not relevant and does not add any information to the central question of the study. I would start with table 2. The authors present four different multivariable models. They do not detail the different influences of the significant variables in the model. For example, it would be interesting to see what happened to the essential variables (hypotension or anemia that are highly correlated with AKI) in the model. Nor do the authors detail their statistical and methodological treatment in multivariable model issues like interaction and multicollinearity. As to the conclusions – I would be more careful in declaring that parecoxib is renoprotective. I think the best we can expect from a retrospective study with a very heterogeneous population is to state that the use of parecoxib did not cause AKI and may hint at a protective effect. I think study limitations should go into more depth regarding selection bias.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1…….Thank you very much for the hard work in this manuscript.

The authors discussed an important topic which is: Drugs that can prevent or reduce incidence of AKI after non-cardiac surgery.

The results are very interesting results; they found that Parecoxib can have protective effect against post-operative AKI.

A: We thank the Reviewer for the comments and have addressed the Reviewer's other concerns below.

2. Abstract:

(1)-The aim of the study is not clear in the abstract. It needs to be clear and easily identified. This is not the case

A: Thanks for your advice! We added the aim of our study in the revised manuscript (Page 2, Main Document - marked copy)

(2)-In the methodology, you wrote that you did logistic regression. However, in the results section, you are talking about incidence! The results section should reflect the methodology. You need to talk about the results of your logistic regression, not the incidence

A:Thanks for your advice! We rewrote the results section in the revised manuscript (Page 2, Main Document - marked copy)

Introduction:
The introduction is generally well written. Some Typos that need to be corrected. I would suggest to write more about how NSAIDs can cause AKI as this is an important point in your debate.
A: Thanks for your suggestion! We added the possible cause of AKI by NSAIDs (page 4, Main Document - marked copy)

Methodology:
(1)-What was the indication of giving Parecoxib? Was it based on the anaesthesia doctor choice?
A: Yes, it based on the doctor choice.

(2)-Why the control group didn't receive Parecoxib Was it a doctor or patient preference?
A: Yes, it was a doctor preference.

(3)-Did the control group receive any other NSAIDs? like Ibuprofen or Naproxen? How many patients receive these medications? These might be a cause that these patients had a higher incidence of AKI?
A: In the control group, patients didn't receive any other NSAIDs.

(4)- The above points can cause a confounding by indication, which is a major limitation in the study.

A: Parecoxib is commonly used perioperative anesthetic adjuvants, with anti-inflammatory and analgesic effects. Whether to use it or not is up to the doctor's personal choice. In our control group, no patients received NSAIDs. So we didn't have the confounding factors mentioned above.

5-Thank you for doing multiple imputation for missing data. However, you need to describe more about the details of multiple imputation. What are the variables you made multiple imputations for? And what are the co-variates used for each imputed variable? You need to write more details about this
A: Thanks for your suggestion! The missing data of covariates we handled by multiple imputation model were BMI and eGFR. We added this information in Statistical analysis part (Page 7, Main Document - marked copy)

6-You need to describe more about your sensitivity /subgroup analysis in the methodology section. What type of sensitivity analysis did you do? Why did you choose these subgroups? What analysis have you done?
A: Thanks for your suggestion! We added these information in the methodology section (Page 7, Main Document - marked copy).

7-I appreciate in the results section, you did some sensitivity /subgroup analysis about non-smoker, eGFR less than 90….Thank you for that
As a Nephrologist, every one working in the Nephrology field knows that the main reason for post-operative AKI is blood loss and hypotension.
I appreciate these are variables you have adjusted for in your logistic regression, however, I would be very interested to know the effect of Percoxib on a subgroup of patients that had intra-operative hypotension/ significant blood loss alone, and another subgroup, among those who didn't have hypotension/significant blood loss. This would make more sense to me and would be more important results as a nephrologist. If the Percoxib showed a protective effect in these subgroups, and the control group, didn't receive any other NSAIDs, then I might believe your results. And this will add more strength to it.

A: We thank the Reviewer for the comments. We added subgroup analysis about intra-operative hypotension and significant blood loss. The results showed, parecoxib still associated with the reduced risk of AKI in the subgroups of non-hypotension and blood loss<1000ml (Page19-20, Main Document - marked copy).

8- Thanks for using the KDIGO as a guide to define AKI. I would like to point out that, from the renal point of view, Nephrologists would be much more interested in AKI stage 2 and AKI stage 3. I would suggest to do a sensitivity analysis having your outcome of measurement as AKI3 and see if Pericoxib will reduce this or not?
A: Thanks for your suggestion! We did sensitivity analysis in table3. Compared with stage 0, parecoxib still associated with the reduced risk of AKI in stage 2 or stage 3 group (Page18, Main Document - marked copy).

Results:
1- In figure 1, is it the number of excluded patients? It is not clear on the figure what are these numbers. You need to write it down.
A: YES, The numbers in brackets represented patients excluded for the reasons described earlier. I added this information in figure legend.

2- You need to write down a table summary for the type of surgical operations done and number of patients, if possible.
A: We did summarize the surgical type and patients' number, but we didn't put this table into manuscript.

Surgical type without AKI(n=8686) With AKI(n=560) <0.001
General surgery 2565(29.53%) 134(24.01%)
urinary surgery 1559(17.95%) 138(24.70%)
gynecological operation 988(11.37%) 281(5.01%)
orthopedic surgery 1614(18.58%) 76(13.65%)

3- It is obvious from table 1 that the AKI patients had significantly higher percentage of intra-operative hypotension and significant blood loss (>1000ml). For any nephrologist, this would be the main and very obvious cause of AKI. Can you please explain your thoughts how Pericoxib can be protective in patients with significant blood loss and intra-operative hypotension? Definitely, you need to do subgroup analysis among these patients. I would be really interested to see your results in these subgroups!
A: Thanks for your suggestion! We added subgroup analysis about intra-operative hypotension and significant blood loss. The results showed, parecoxib still associated with the reduced risk of AKI in the subgroups of non-hypotension and blood loss<1000ml (Page19-20, Main Document - marked copy).

4- Table 1 is too big, can go to supplementary data.
A: Thanks for your suggestion! We put Table 1 into supplementary data.

5- I just don't understand table 5 or your sensitivity analysis! It is not clear in the methodology or in the results. Please clarify
A: Sorry for the confusion. We rewrote this part in the revised manuscript (Page 7, Page19-20, Main Document - marked copy)

6- I slightly disagree with your classification for AKI rank. You need to separate AKI 2 from AKI 3 (as per KDIGO guidelines)
A: Thanks for your suggestion! We separate AKI 2 from AKI 3 in the revised manuscript (Page18, Main Document - marked copy).

Discussion:
1- The limitation part is limited. Please use the comments above to expand in your limitations.
A: Thanks for your suggestion! We expand the limitation part (Page23, Main Document - marked copy)

2-You need to write down the names of the studies you are discsussing, perhaps use the first author name, rather than saying: a study!
A: Thanks for your suggestion! I added the first author name from the references in the discussion part (Page 20-22, Main Document - marked copy).

Reviewer: 2
……This large study has interesting results and sound methodology.I have a few questions and comments.
A: We thank the Reviewer for the comments and have addressed the Reviewer's other concerns below.

1…….Why did the authors include ASA 4 patients in the study? These patients are high-risk patients, and I think that many of their surgeries are emergent. Many studies refrain from using ASA 4 patients. What were the author's considerations?
A: Thanks for this suggestion. We included ASA 4 patients not only to reduce the selection bias, but also to expand the study population.

2. Why did the authors exclude any use of surgeries with the use of local anesthetics? Moreover, the authors mention that a certain percentage of the patients were operated not under general anesthesia. If no local anesthetics were used, how were the non-general anesthesia patients operated on?
A: Sorry for the confusion. The excluded patients with local anesthetics means the surgeon administered regional anaesthesia by himself. The anesthesiologist was not involved. We revised this in the Fig1 and results part (Page 8, Main Document - marked copy). In our selected patients, non-general anesthesia means neuraxial anesthesia (spinal or epidural) and nerve block anesthesia. We added this information in the description of the table(Page 11,14,16, Main Document - marked copy).

3. In row 105, the authors mention that the preoperative Cr was defined as the lowest level at preoperative day 7. Can the authors clarify this sentence? Were all the patients hospitalized more than seven days before the surgery? If not – from where were the Cr levels obtained?
A: We are sorry about the mistake. The preoperative Cr was defined as the lowest level within preoperative day 7. We corrected in the revised version (Page 6, Main Document - marked copy).

4. How was baseline CKD defined? From medical records or calculated from the Cr, BMI and gender?
A: We defined baseline CKD in the methods part (page 5, Main Document - marked copy). The preoperative combined CKD defined as eGFR <60 mL·min-1·1.73m(2) -1, ≥3 months

5. In my opinion, table 1 is not relevant and does not add any information to the central question of the study. I would start with table 2.
A: Thanks for your suggestion! We put table 1 in the supplement data.

6. The authors present four different multivariable models. They do not detail the different influences of the significant variables in the model. For example, it would be interesting to see what happened to the essential variables (hypotension or anemia that are highly correlated with AKI) in the model. Nor do the authors detail their statistical and methodological treatment in multivariable model issues like interaction and multicollinearity.
A: Thanks for this advice. We add the sensitivity analysis about the subgroups of hypotension and significant blood loss (Page19, Main Document - marked copy). On multivariate logistic regression, no significant collinearity was identified for any of the covariates in the statistical tests of collinearity.

7. As to the conclusions – I would be more careful in declaring that parecoxib is renoprotective. I think the best we can expect from a retrospective study with a very heterogeneous population is to state that the use of parecoxib did not cause AKI and may hint at a protective effect.
A: Thanks for this advice. We will come to the conclusion more carefully. And the conclusion was corrected (Page2, Page 24, Main Document - marked copy).

8. I think study limitations should go into more depth regarding selection bias.
A: Thanks for your suggestion. We have strengthened the description of the limitations of the article (Page 23, Main Document - marked copy).

VERSION 2 – REVIEW

REVIEWER	Hatem Ali University Hospitals Birmingham NHS Foundation Trust
REVIEW RETURNED	03-May-2021

GENERAL COMMENTS	The manuscript is much better. I like the subgroup analysis for patients with minimal blood loss and patients with no intra-operative hypotension. The results are interesting. Few typos and grammatical errors needs correction Also, please write clearly in the manuscript that the choice of NSAID was based on doctor preference. This needs to be clear

REVIEWER	O Goren Tel Aviv Sourasky Medical Center
REVIEW RETURNED	12-May-2021

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Dr. Hatem Ali, University Hospitals Birmingham NHS Foundation Trust

Comments to the Author:

The manuscript is much better.

I like the subgroup analysis for patients with minimal blood loss and patients with no intra-operative hypotension.

The results are interesting.

Few typos and grammatical errors needs correction

A: We thank the Reviewer for the comments and have corrected some typos and grammatical errors in the new manuscript.

Also, please write clearly in the manuscript that the choice of NSAID was based on doctor preference.

This needs to be clear

A: Thanks for your advice! We added the information in the methods part. (Page 5, Main Document - marked copy)