PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

C-reactive protein in the first 30 postoperative days and its discriminative value as a marker for postoperative infections, a multi-center cohort study

Authors

van Boekel, Anna Marthe; van der Meijden, Siri Lise; Geerts, Bart F.; van Goor, Harry; van Geloven, Nan; Arbous, Mendi S.; de Boer, Mark G.J.; study group, The PERISCOPE

VERSION 1 - REVIEW

Reviewer	**1**
Name	**Kuemmerli , Christoph**
Affiliation	**Clarunis University Center for Gastrointestinal and Liver Diseases, Department of Surgery**
Date	**02-Nov-2024**
COI	**None**

The authors present a large case series including mostly basic data from two Dutch centers aiming at constructing an association between CRP and infections.

The report is well-written and I congratulate the authors. Some comments are listed below:

What is the rationale for the CRP categories and week intervals?

When you include CRP after the initiation of an “antiinfectious” therapy, what is the value of CRP in the management of the patient?

I am not sure if you can infere causality based on the week-wise grouping. Can you elaborate on this?

Please add the number of excluded patients for all categories that you mention in the first results paragraph.

Minor

I suggest that molecular descriptions of CRP are omitted.

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Reviewer 2

Name Dong, Hailong

Affiliation Fourth Military Medical University, Department of Anesthesiology and Perioprative Medicine, Xijing Hospital

Date 02-Nov-2024

COI None

The authors investigated the association of postoperative C-reactive protein (CRP) and 30-d postoperative infection by using more than 40,000 surgcial procedures from 2 tertiary centers in Netherland. By using the big data, this retrospective study give us some information and evidence regarding the relative biomarker for postoperative infections. However, I have identified several shortcomings and limitations regarding the research question, data analysis, and interpretation of results that I believe should be addressed to strengthen the manuscript.

1.Research Question Clarity: The research question could benefit from further refinement. As CRP has long been regarded as an index for inflammatory responses for critical patients, when what is the clinical relevence for this study. What is the knowledge gap that this study aimed to address? While the study aims to assess the discriminative value of CRP in detecting postoperative infections, it would be helpful to specify the types of infections being investigated (e.g., surgical site infections, systemic infections), and the timepoint for CRP measurement. A clearer definition of the clinical context would enhance the relevance of the research question.

2.It was stated that “surgical intervention for an infection such as drainage and re

operation within 30 days of the index surgery”, then how to distingush surgical intervention for bleeding or for infection?

3.The statistical methods employed for analyzing the data need to be described in greater detail. Specifically, it would be beneficial to clarify how you handled missing data and whether any sensitivity analyses were conducted to assess the robustness of your findings. The stratification of CRP by 5 mg/dl was based on clinical expertise or data? As I know CRP was a skewed data, the data should be transformed to fit the normality.

4.The study mixed association analysis and prediction. And as retrospective data, no adjustment for confoundings were made, such as patient demographics, comorbidities, surgical procedures, and the timing of CRP measurements relative to surgery. In additon, from the manuscript, it is hard to say the which happened first, the increase of CRP or the infection. In other word, it is hard to say if there was reversal causal effect.

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Reviewer	**3**
Name	**Zheng, Ziyu**
Affiliation	**Lancaster University, Department of Anesthesiology and Perioperative Medicine**
Date	**02-Nov-2024**
COI	**None**

MAJOR:

What are postoperative infections, please define?

Should different types of infections or severity of infections be considered?

Were any of the individual comorbidities such as diabetes considered?

Surgical information such as operation levels, anesthesia types, durations and whether precautious treatments for infections were used should be of concern as well. I would consider them as huge confounding factors. They should at least be discussed and adjusted for before any statistical inference.

For subgroup analysis, if you suggested that CRP levels indicate differently for different surgeries. Please report p-for-interaction as well.

What is the abbreviation of CRP for? Should it be explained in full before first used?

Abstract: should be self-explanatory standing on its own. It is very ambiguous without reading the whole article.

Setting: not clear

Participants: ambiguous. It is hard to gasp as what you mean by “A total of 42,125 surgical procedures from 40,009 unique patients were included.” without reading the article. Why would the number not match and why should there be more procedures than patients.

Results: Please report OR as point estimate and 95%CI. Also be more specific for “stronger” or “more time”. What are the point estimates and 95%CI.

“Patients could be included more than once when they underwent multiple surgeries within the period of study.” This is likely to introduce individual bias where the specific personnel is likely to be infected if previously developed infections. Sensitivity analysis should be conducted on this, or intercorrelation should be adjusted using modelling techniques.

The patients were grouped according to outcomes (Table 1 and as described in method). This is not typically recommended. Comparisons between baselines for whether the event occurred are then equivalent to univariate analysis.

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Why was CRP-range semented in such manner? If CRP's not treated as a continuous variable, Table 1 should be comparing each segment of CRP. Details on this please refer to STROBE guidlines.

How was the missing data handled? Please specify

I found it hard to match the numbers, for example in results section, it says 175,779 measurements, then 170,791 measurements. Please check accuracy.

Reviewer	**4**
Name	**Yang, Liqun**
Affiliation	**Shanghai Jiao Tong University School of Medicine, Anesthesiology**
Date	**04-Nov-2024**
COI	**None**

This article addresses the association of CRP levels with postoperative infection within follow-up 30 days using big data. The definition of postoperative infection is supported by previous study. The authors reveal the diagnostic value of CRP by different CRP levels and time elapsed since surgery with appropriate statistical analyses. The article is well organized and presentation is good for publication.

VERSION 1 - AUTHOR RESPONSE

Response to reviewer 1:

Dr. Christoph Kuemmerli , Clarunis University Center for Gastrointestinal and Liver Diseases

The authors present a large case series including mostly basic data from two Dutch centers aiming at constructing an association between CRP and infections.

The report is well-written and I congratulate the authors. Some comments are listed below:

What is the rationale for the CRP categories and week intervals?

Thank you for addressing this importing issue. To enhance the statistical power and maintain a comprehensive statistical analysis we divided the CRP values in categories and week-intervals. Because we used retrospective data, we did not have CRP measurements at standard moments postoperatively. Without dividing the CRP values in categories and per week intervals there would have been too many different CRP moment and value

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combinations. Moreover, we aimed to present outcomes that clinicians can relate to in daily clinical practice. From that perspective, CRP-ranges spanning 5mg/dL per category and looking at weekly intervals, seemed a reasonable approach.

When you include CRP after the initiation of an “anti-infectious” therapy, what is the value of CRP in the management of the patient?

We understand the question of the reviewer, but there is a logical explanation for the way the analyses were handled. The primary research question is to which extent CRP can be used as a predictive marker for post-operative infection. Therefore, CRP values measured after the start of anti-infectious therapy are not included in the analysis, see also supplementary eFigure 1. If this would have been the case, it did not have a ‘predictive purpose’ but may be used for the management of infection. This is something we intent to explore in another study

I am not sure if you can infere causality based on the week-wise grouping. Can you elaborate on this?

We agree with the reviewer that this should be addressed as obviously we do wish to infere causality. A postoperative infection can cause a rise in CRP. As the diagnosis of infection is difficult, markers such as CRP are used to make an infection more of less plausible. In this study we showed the relation between CRP and a postoperative infection, and that a rise in CRP can be seen as a sign of postoperative infection. The hight of the CRP and the week postoperative determine the strength of this sign of infection.

As a standard – and this is what most studies about post-operative markers do – the results are presented as a total over the period of interest (i.e. 30 days postoperative in this study). In our study, the results are presented per week, which shows a marked difference between the weeks. This can be further split up in ½ weeks or per day, showing a similar pattern, but with more limited accuracy. However, splitting up the results per week does not show any causality as CRP cannot cause a postoperative infection but is only a sign of infection.

Please add the number of excluded patients for all categories that you mention in the first results paragraph.

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We have added the number of excluded patients for each exclusion reason in the results section.

Minor

I suggest that molecular descriptions of CRP are omitted.

We understand the comment of the reviewer and have shortened the introduction paragraph about CRP.

Response to reviewer 2

Prof. Hailong Dong, Fourth Military Medical University

The authors investigated the association of postoperative C-reactive protein (CRP) and 30-d postoperative infection by using more than 40,000 surgical procedures from 2 tertiary centers in Netherland. By using the big data, this retrospective study give us some information and evidence regarding the relative biomarker for postoperative infections. However, I have identified several shortcomings and limitations regarding the research question, data analysis, and interpretation of results that I believe should be addressed to strengthen the manuscript.

Research Question Clarity: The research question could benefit from further refinement. As CRP has long been regarded as an index for inflammatory responses for critical patients, when what is the clinical relevance for this study. What is the knowledge gap that this study aimed to address? While the study aims to assess the discriminative value of CRP in detecting postoperative infections, it would be helpful to specify the types of infections being investigated (e.g., surgical site infections, systemic infections)and the timepoint for CRP measurement. A clearer definition of the clinical context would enhance the relevance of the research question.

Thank you for this constructive remark. We have adjusted the introduction to further explicate the knowledge gap (i.e. clinical dilemma), the research question and its clinical relevance.

All types of postoperative infections were included in this study, the exact definition we used to identify a postoperative infection is described in the methods section.

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It was stated that “surgical intervention for an infection such as drainage and re operation within 30 days of the index surgery”, then how to distinguish surgical intervention for bleeding or for infection?

The indications for re-operation and drainage were manually checked in the electronic health record of the patients based on the ICD10 codes or other hospital specific diagnostic codes. This way we could distinguish between interventions for an infection versus another reason. The procedure how we have checked this is described in the methods section.

The statistical methods employed for analyzing the data need to be described in greater detail. Specifically, it would be beneficial to clarify how you handled missing data and whether any sensitivity analyses were conducted to assess the robustness of your findings. The stratification of CRP by 5 mg/dl was based on clinical expertise or data? As I know CRP was a skewed data, the data should be transformed to fit the normality.

Thank you for noticing these dilemma’s in the analysis.

In reaction to the first point: when using this data it is indeed important to realise CRP is not measured at random but for a reason, thus missing CRP data was not missing (completely) at random. We therefore did not impute missing values and decided to accept the missing data in our analysis. We have slightly extended the methods section on missing data to make this clearer. Moreover, from a clinical perspective it would make less sense to impute because we aimed to base our findings on data from real-life clinical practice.

With respect to your second remark: the stratification of CRP by 5mg/dl was indeed based on clinical expertise. During this study we consulted different clinical specialists (namely an infectious disease specialists, intensive care specialists and surgeons), and by expert discussion we came to the CRP groups stratified by 5mg/dl.

In reaction to the last point, CRP is indeed a skewed marker and when used as a continuous marker in a logistic regression it should be transformed as the model assumes CRP has a normal distribution. However, we did not use CRP as a continuous marker but divided the

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patients in CRP groups. When analysing a skewed marker as a categorised variable transformation is not needed (Grund and Sabin 2010).

Based on the comments of the reviewer we have extended the statistical analysis paragraph of the methods section.

The study mixed association analysis and prediction. And as retrospective data, no adjustment for confoundings were made, such as patient demographics, comorbidities, surgical procedures, and the timing of CRP measurements relative to surgery. In additon, from the manuscript, it is hard to say the which happened first, the increase of CRP or the infection. In other word, it is hard to say if there was reversal causal effect.
We agree with the reviewer that our study does indeed have shortcomings, which is also due to the high number of included surgeries and its retrospective design. We minimalized the effects of these limitations by excluding the CRP measurements done one week before start of the anti-infectious therapy.

Furthermore, the aim of this study was to evaluate the value of CRP as a diagnostic tool in clinical practice. And a high CRP itself does not cause infection, but an infection can cause a high CRP. Whether a high CRP made physicians believe that there was an infection and start antibiotics, while there was in fact no infection, cannot be retraced. We were conscious of this potential mechanism and therefore specified in the infection definition to include only antimicrobials started for a duration of at least 3 days.

Besides, even in a prospective study it is impossible to identify the exact start of an infection. Moreover, due to the high amount of data, we believe that the general correlation of a higher CRP postoperatively and a postoperative infection can be concluded. Furthermore, as we used data from two different hospitals, with both the same relation between CRP and postoperative infections, this further enhances the robustness of the findings in this study.

Response to reviewer 3

Miss Ziyu Zheng, Lancaster University

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MAJOR:

What are postoperative infections, please define?

In the methods section the definition that we used to define postoperative infections is described as follows:

'As there is under-registration of complications in real-life clinical practice15, a clinical action-based definition of postoperative infection was used in which postoperative infections were defined as the start of non-prophylactic antibiotics (initiated >24 hours postoperatively and with a minimum duration of 72 hours) and/or a surgical intervention for an infection such as drainage and re-operation within 30 days of the index surgery. All types of postoperative infections were included. See eTable 2 in the Supplement for the full definition used for postoperative infection.'

Should different types of infections or severity of infections be considered?

Thank you for this suggestion. It would be interesting to see if severity of infection or type of infection would lead to different results. With the data we used and the definition we used to define postoperative infection it is not possible to make subgroups based on type of postoperative infection or severity of postoperative infection for further analysis.

Were any of the individual comorbidities such as diabetes considered?

In this study we did not included comorbidities of the patients in the analysis. It is known that some comorbidities can cause an elevated CRP and also increase the risk for infection. Due to the high amount of included patients in combination with the retrospective design of the study it was not possible to include comorbidities in the analyses

Surgical information such as operation levels, anesthesia types, durations and whether pre-cautious treatments for infections were used should be of concern as well. I would consider them as huge confounding factors. They should at least be discussed and adjusted for before any statistical inference.

Thank you for mentioning possible confounders. Confounding is an important issue in etiological studies. This study is not an etiological study as, an elevated CRP is the effect of an infection, but cannot cause an infection itself. In prediction studies, there is no

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confounding, but more predictors could have been used if we had wanted to predict postoperative infection. However, we did not aim to make a prediction model for postoperative infections but wanted to analyse the diagnostic value of CRP in clinical practice. Therefore, we have only looked at CRP without correcting for other factors. To examine the value of CRP in the diagnosis of postoperative infections in different surgical specialties we did do a subgroup analyses for eight different surgical specialties.
We have added a section in the discussion were we further explain why we did not adjust for other prognostic factors in the analysis.

For subgroup analysis, if you suggested that CRP levels indicate differently for different surgeries. Please report p-for-interaction as well.
Thank you for addressing this point. An interaction term is a statistical term, usually used in etiological research. Our study is not an etiological study but a diagnostic study. Moreover, the variable 'surgical specialty' is difficult to define in an interaction term. We have therefore chosen to report the results per surgical specialty. We believe that this way of presenting the results gives sufficient insight of the value of CRP in the different surgical specialties to answer our diagnostic question and help clinicians to interpret their CRP results.

What is the abbreviation of CRP for? Should it be explained in full before first used?
Thank you for observing the first time CRP was used in the abstract, the abbreviation was not written out full out. We have adjusted this.

Abstract: should be self-explanatory standing on its own. It is very ambiguous without reading the whole article.
Thank you for addressing that the abstract is not self-explanatory on its own. We have adjusted the abstract to make it more easily to understand without reading the whole article.
Setting: not clear

Participants: ambiguous. It is hard to gasp as what you mean by "A total of 42,125 surgical procedures from 40,009 unique patients were included." without reading the article. Why would the number not match and why should there be more procedures than patients.

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We have adjusted the abstract to make it more self-explanatory.

Results: Please report OR as point estimate and 95%CI. Also be more specific for “stronger” or “more time”. What are the point estimates and 95%CI.

We agree, the results section of the abstract is now updated with the ranges of the numerical data for the reported findings. Due to the large amount of results, we did not report all the 95%CI in the abstract results section, we refer to the main manuscript and eTable 4 for a complete overview of the results.

“Patients could be included more than once when they underwent multiple surgeries within the period of study.” This is likely to introduce individual bias where the specific personnel is likely to be infected if previously developed infections. Sensitivity analysis should be conducted on this, or intercorrelation should be adjusted using modelling techniques.

Patients could be included more than once but only if they met several conditions; the second surgery could not be a surgery done because of an infection, the CRP pre-operative had to be <2.5mg/dL, and the second surgery could not be within 30 days of the previous surgery. Moreover, we included more than 45,125 surgical procedures from 40,009 unique patients in a time span of almost 12 years. Therefore, risk factors that might have contributed to the infection after the first surgery can be completely different for the second surgery. We agree with the reviewer, there is a small possibility the patient has specific risk factors that increase their risk for a second postoperative infection. However, these risk factors should also alter the relationship between infection and CRP to be of any importance for the final results. We therefore believe these few cases will not alter the results of complete study, especially with the large amount of surgeries included.

The patients were grouped according to outcomes (Table 1 and as described in method). This is not typically recommended. Comparisons between baselines for whether the event occurred are then equivalent to univariate analysis.

Thank you for this question. We agree with the reviewer that in some cohort studies the outcomes are grouped by exposure instead of outcome. However, whether this is possible depends on the research question and available data. There are multiple reasons why have chosen not to compare CRP groups in table 1.

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First of all, CRP cannot be considered as a real exposure. An elevated CRP is a reaction of the body to inflammation. In other words, an elevated CRP is a result of infection but does not cause an infection. Because infection is very difficult measure, CRP is used as a surrogate marker for infection and for that reason not an exposure. The second reason is practicability. In this study, CRP is divided into five different groups and in four different weeks. One patient can be in one group the first week and in another group the next week. Consequently, table 1 will consist of 20 different groups when grouped by CRP and week, which will be unclear.

Why was CRP-range segmented in such manner? If CRP's not treated as a continuous variable, Table 1 should be comparing each segment of CRP. Details on this please refer to STROBE guidlines.

Thank you for addressing this importing issue. To enhance the statistical power and maintain a comprehensive statistical analysis we divided the CRP values in categories and week-intervals. Because we used retrospective data, we did not have CRP measurements at standard moments postoperative. Without dividing the CRP values in categories and per week intervals there would have been too many different CRP moment and value combinations. Moreover, we aimed to present outcomes that clinicians can relate to in daily clinical practice. From that perspective, CRP-ranges spanning 5mg/dL per category and looking at weekly intervals seemed a reasonable approach.

In response to the comments about Table 1 see our answer to the previous question.

How was the missing data handled? Please specify

When using this data it is indeed important to realise CRP is not measured at random but for a reason, thus missing CRP data was not missing (completely) at random. We therefore did not impute missing values and decided to accept the missing data in our analysis. We have slightly extended the methods section on missing data to make this clearer. Moreover, from a clinical perspective it would make less sense to impute because we aimed to base our findings on data from real-life clinical practice.

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I found it hard to match the numbers, for example in results section, it says 175,779 measurements, then 170,791 measurements. Please check accuracy.

Thank you for noticing this. The first number is the number of CRP measurements done in the first 30 days postoperatively. The second number is the number of CRP measurements included in the analysis. The difference between these numbers is caused by the exclusion of CRP values when multiple CRP measurements were done at the same day. Only the maximum CRP value of the day was included in the analyses. We agree it could be specified more clearly what these numbers mean, and why the last ~5000 measurements were excluded, we have adjusted this in the results section.

Reviewer: 4

Dr. Liqun Yang, Shanghai Jiao Tong University School of Medicine

Comments to the Author:

This article addresses the association of CRP levels with postoperative infection within follow-up 30 days using big data. The definition of postoperative infection is supported by previous study. The authors reveal the diagnostic value of CRP by different CRP levels and time elapsed since surgery with appropriate statistical analyses. The article is well organized and presentation is good for publication.

Reviewer: 1

If you have selected 'Yes' above, please provide details of any competing interests.: Not applicable

Reviewer: 2

If you have selected 'Yes' above, please provide details of any competing interests.: Not applicable

Reviewer: 3

If you have selected 'Yes' above, please provide details of any competing interests.: Not applicable

Reviewer: 4

If you have selected 'Yes' above, please provide details of any competing interests.: Not applicable.

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References

Grund, B. and C. Sabin (2010). "Analysis of biomarker data: logs, odds ratios, and receiver operating characteristic curves." Curr Opin HIV AIDS **5**(6): 473-479.

VERSION 2 - REVIEW

Reviewer	**1**
Name	**Kuemmerli , Christoph**
Affiliation	**Clarunis University Center for Gastrointestinal and Liver Diseases, Department of Surgery**
Date	**15-Jan-2025**
COI	

No further comments

Reviewer	**2**
Name	**Dong, Hailong**
Affiliation	**Fourth Military Medical University, Department of Anesthesiology and Perioprative Medicine, Xijing Hospital**
Date	**15-Jan-2025**
COI	

I have not more questions with the revised manuscript. However, some typos needs to be correct.

Reviewer	**3**
Name	**Zheng, Ziyu**
Affiliation	**Lancaster University, Department of Anesthesiology and Perioperative Medicine**
Date	**22-Jan-2025**
COI	

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Thank you for the thorough response from the authors, I am happy with the majority. However, I still think that some clarifications would be beneficial in terms of clearer presentation.

Minor:

Regarding the confounding issues, exactly what I meant, as if you fail to account for confounders such as age, sex, or comorbidities (which might also influence the disease outcome), the association could be biased. You should at least discuss this point in the discussion or strength and limitation parts if it is not possible to include in the analysis.

Also perhaps the point should be stressed out stating that as this study is primarily focused on evaluating the diagnostic value of CRP for detecting postoperative infection in clinical practice. As such, the aim was to assess the sensitivity and specificity etc, not to explore the underlying causes of infection or predict infection outcomes

At the same time, subgroup analyses across different surgical specialties for example should also be an important point because it shows that while confounders weren't adjusted for, the study still aimed to ensure the generalizability and clinical relevance of the findings across different types of surgeries (or any other clinically important stratification). It certainly can help explore variations in diagnostic value of CPR in different settings. Especially if you have already done some explorations on this.

VERSION 2 - AUTHOR RESPONSE

Reviewer: 1

Dr. Christoph Kuemmerli , Clarunis University Center for Gastrointestinal and Liver Diseases

Comments to the Author:

No further comments

Reviewer: 2

Prof. Hailong Dong, Fourth Military Medical University

Comments to the Author:

I have not more questions with the revised manuscript. However, some typos needs to be correct.

Thank you for noticing some typos in the manuscript. We now have corrected all typos.

Reviewer: 3

Miss Ziyu Zheng, Lancaster University

Comments to the Author:

Thank you for the thorough response from the authors, I am happy with the majority. However, I still think that some clarifications would be beneficial in terms of clearer presentation.

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Minor:

Regarding the confounding issues, exactly what I meant, as if you fail to account for confounders such as age, sex, or comorbidities (which might also influence the disease outcome), the association could be biased. You should at least discuss this point in the discussion or strength and limitation parts if it is not possible to include in the analysis.

Thank you for further clarifying this point. We agree that the level of CRP as well as the risk of infection can be influenced by age, comorbidities, and use of certain medications. In certain subgroups this may have influenced the strength of the association between CRP and postoperative infections. In the limitations section of our manuscript, we mentioned the possible influence of an elevated preoperative CRP due to comorbidities. We have now expanded this part of the limitation section (page 13) to emphasize that not only pre-operative CRP can be altered by comorbidities but also the relation between CRP and postoperative infection could be different in patients with different comorbidities, age, or medication use.

Also perhaps the point should be stressed out stating that as this study is primarily focused on evaluating the diagnostic value of CRP for detecting postoperative infection in clinical practice. As such, the aim was to assess the sensitivity and specificity etc, not to explore the underlying causes of infection or predict infection outcomes

We thank the reviewer for this comment and have rephrased the sentence that outlines the purpose of this study in the introduction: *" The aim of this study was to obtain insight into the clinical use of CRP and its potential diagnostic value as a biomarker for the diagnosis of any type of postoperative infection".*

At the same time, subgroup analyses across different surgical specialties for example should also be an important point because it shows that while confounders weren't adjusted for, the study still aimed to ensure the generalizability and clinical relevance of the findings across different types of surgeries (or any other clinically important stratification). It certainly can help explore variations in diagnostic value of CPR in different settings. Especially if you have already done some explorations on this.

Thank you for your comment. We agree with the reviewer that further exploration of different subgroups would be interesting. Unfortunately, we are not able to analyse subgroups related to comorbidity or medication use due to the heterogeneity within these factors and the lack of availability of data on subgroup membership. We addressed this limitation in the discussion (page 13).

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