PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Post-Cholecystectomy diarrhoea rate and predictive factors – a systematic review of the literature
AUTHORS	Farrugia, Alexia; Attard, Joseph Anthony; Khan, Saboor; Williams, Nigel; Arasaradnam, Ramesh

VERSION 1 – REVIEW

REVIEWER	Ewen Griffiths University Hospitals Birmingham NHS Foundation Trust, Department of Upper GI Surgery
REVIEW RETURNED	24-Nov-2020

GENERAL COMMENTS	Thanks for asking me to review this paper on an important and understudied complication of cholecystectomy - diarrhoea. This systematic review was prospectively registered on PROSPERO The studies included have some severe limitations which are fully acknowledged by the authors - which are short followup periods, lack of a control group (majority of studies are not RCTs), patient recall biasis and nonstandardised assessment of symptoms, and overall low quality of evidence. Sadly little can be gained from the potential predictors of post-cholecystectomy diarrhoea as the original data is so poor and many are conflicting. The authors have gone to alot of effort in to trying to summarise the previous data on this topic and are to be commended on this. They extensively discuss the potential mechanisms for this complication in the discussion. My commments are 1. They come up with a clinical definition of post-cholecysectomy diarrhoea in the discussion, however its unclear whether this is evidence based or from the literature they have reviewed. This should be clarified. Did the studies included have other definitions?? 2. 'Article Summary – Strengths and limitations of this study' are poor in my opinion and this could be significantly improved to show what the authors have achieved and the limitations of the research summarised. 3. I wonder where there is any more data that can be extracted from the original papers. They seem pretty scanty on detail. Even numbers of males / females, summary age range etc, % of no of laparoscopic cholecystectomy versus open or details of indication for

BMJ Open: first published as 10.1136/bmjopen-2020-046172 on 17 February 2022. Downloaded from http://bmjopen.bmj.com/ on November 5, 2024 by guest. Protected by copyright.

	surgery etc could be added. What investigations did the patients get to investigate diarrhoea in each study??? Could this be added??? 4. There appears to be previous systematic review on this topic which is not discussed or referenced Aliment Pharmacol Ther . 2019 Feb;49(3):242-250. doi: 10.1111/apt.15099. Epub 2018 Dec 25. Systematic review with meta-analysis: the prevalence of bile acid malabsorption and response to colestyramine in patients with chronic watery diarrhoea and previous cholecystectomy Laura Ruiz-Campos 1, Javier P Gisbert 2 3, Montserrat Ysamat 4, Beatriz Arau 1, Carme Loras 1 3, Maria Esteve 1 3, Fernando Fernández-Bañares 1 3 4. There is probably too much discussion on the mechanisms of bile acid diarrhoea post cholecystectomy. I can see why the authors have done this as the original data is pretty unsatisfactory, but i think it is perhaps too much (as its little to do with the data they actually extracted from the systematic review) and the authors should consider cutting this down.

REVIEWER	Andrea Costanzi ASST di Lecco, Surgery
REVIEW RETURNED	13-Jan-2021

GENERAL COMMENTS	The study is well designed and conducted. However it leads to poor evidence, offers only a rough estimate of the problem and doesn't help to understand neither its etiology nor its consequences. When the authors describe implications for future research I would expect the proposal of an investigation on the rate of post-cholecystectomy diarrhoea, predictive factors and implications on QOL conducted by the same authors who came to the conclusions of lack of evidence in the form of a multicentre prospective study rather than a national registry, much more complex to set up.

REVIEWER	Francesco Mongelli Lugano Regional Hospital, Surgery
REVIEW RETURNED	18-Jan-2021

GENERAL COMMENTS	Thank you for the possibility to review the article “Post-Cholecystectomy diarrhoea rate and predictive factors – a systematic review of the literature”. There are some points that need to be addressed before considering for publication. An English review is needed. Introduction The actual incidence of PCD is not unknown as the studies included in the present meta-analysis reported it. Authors should mention the reported range of incidence in the literature. The aim of the article should be the rate of PCD only (incidence, not the prevalence I guess). Preoperative factors and pathophysiological mechanisms can be reported by a merely descriptive point of view and should not mandatorily be mentioned in study aim. I would add a paragraph which include the definition of PCD, timing of onset, resolution of symptoms and therapies in brief.

BMJ Open: first published as 10.1136/bmjopen-2020-046172 on 17 February 2022. Downloaded from http://bmjopen.bmj.com/ on November 5, 2024 by guest. Protected by copyright.

	Methods Please indicate the last update of the search (day, month and year when the research has been conducted) Which publication years were considered? No year restriction? That should be mentioned. Primary and secondary endpoints should be better defined. A definition of PCD is mandatory and should include exactly the time range of diarrhea onset after cholecystectomy. The sentence "Studies pertaining to persistent symptoms after laparoscopic cholecystectomy, that is symptoms present pre-operatively, rather than new symptoms were also excluded" is unclear. Statistical methods are completely missing. Results: The section "Characteristics of included studies" should provide more details and reports transparently which study reported which outcome. The level of evidence of this systematic review should be very low. No information is provided regarding resolution of symptoms. Usually PCD lasts very few weeks, it is very uncommon to have long-lasting symptoms. It should be useful to report if in the included studies any kind of preoperative antibiotic therapy was administered. I don't understand why pathophysiological mechanisms are included in the results if they can be only reported by a descriptive point of view. Discussion The reported range of PCD rate among studies is very wide. Do authors have an explanation for that? Study limitations should be better discussed, in particular, heterogeneity. A paragraph to discuss possible therapies (diet, life-style modifications, etc.) is desired. Conclusions are not adequate or pertinent with the core content of the article.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Mr. Ewen Griffiths, University Hospitals Birmingham NHS Foundation Trust Comments to the Author:
Thanks for asking me to review this paper on an important and understudied complication of cholecystectomy - diarrhoea.

This systematic review was prospectively registered on PROSPERO

The studies included have some severe limitations which are fully acknowledged by the authors - which are short followup periods, lack of a control group (majority of studies are not RCTs), patient recall biasis and nonstandardised assessment of symptoms, and overall low quality of evidence.

Sadly little can be gained from the potential predictors of post-cholecystectomy diarrhoea as the original data is so poor and many are conflicting.

The authors have gone to alot of effort in to trying to summarise the previous data on this topic and are to be commended on this. They extensively discuss the potential mechanisms for this complication in the discussion.

My commments are

BMJ Open: first published as 10.1136/bmjopen-2020-046172 on 17 February 2022. Downloaded from http://bmjopen.bmj.com/ on November 5, 2024 by guest. Protected by copyright.

1. They come up with a clinical definition of post-cholecysectomy diarrhoea in the discussion, however its unclear whether this is evidence based or from the literature they have reviewed. This should be clarified. Did the studies included have other definitions??

Response: Most studies do not define PCD and there is no standardised definition. We wanted to set up a standardised definition for PCD to attempt to inform doctors involved in treating patients with PCD. We have attempted to clarify this on page 11.

2. 'Article Summary – Strengths and limitations of this study' are poor in my opinion and this could be significantly improved to show what the authors have achieved and the limitations of the research summarised.

Response: This section has been completely re-written (page 3) and a section has been added to the discussion (page 12).

3. I wonder where there is any more data that can be extracted from the original papers. They seem pretty scanty on detail. Even numbers of males / females, summary age range etc, % of no of laparoscopic cholecystectomy versus open or details of indication for surgery etc could be added. What investigations did the patients get to investigate diarrhoea in each study??? Could this be added???

Response: Thank you. Demographic data has been added, though it was not present in all studies and have made mention of this in the results. However only two studies actually discussed investigating the diarrhoea patients, developed by means other than a questionnaire. The information included can be found in pages 5 and 6 in a subsection of the results entitled 'Demographics'.

4. There appears to be previous systematic review on this topic which is not discussed or referenced

Aliment Pharmacol Ther
. 2019 Feb;49(3):242-250. doi: 10.1111/apt.15099. Epub 2018 Dec 25.
Systematic review with meta-analysis: the prevalence of bile acid malabsorption and response to colestyramine in patients with chronic watery diarrhoea and previous cholecystectomy Laura Ruiz-Campos 1, Javier P Gisbert 2 3, Montserrat Ysamat 4, Beatriz Arau 1, Carme Loras 1 3, Maria Esteve 1 3, Fernando Fernández-Bañares 1 3

Response: Thank you for this reference. Systematic reviews in general were not in the inclusion criteria, however this paper was assessed by us. Unfortunately, studies included in this paper were not relevant to our review as we were not able to elicit a percentage of patients who developed PCD. In fact the studies included in this paper had patients with all causes of diarrhoea and only a percentage of those had prior cholecystectomy. Therefore it did not fit our inclusion criteria. However on further reading of the paper we did find some relevant points which we have now included in our introduction (page 4) and we have referenced the paper accordingly. Thank you for pointing this out.

4. There is probably too much discussion on the mechanisms of bile acid diarrhoea post cholecystectomy. I can see why the authors have done this as the original data is pretty unsatisfactory, but i think it is perhaps too much (as its little to do with the data they actually extracted from the systematic review) and the authors should consider cutting this down.

Response: This has been shortened.

BMJ Open: first published as 10.1136/bmjopen-2020-046172 on 17 February 2022. Downloaded from http://bmjopen.bmj.com/ on November 5, 2024 by guest. Protected by copyright.

Reviewer: 2
Dr. Andrea Costanzi, ASST di Lecco
Comments to the Author:
1. The study is well designed and conducted. However it leads to poor evidence, offers only a rough estimate of the problem and doesn't help to understand neither its etiology nor its consequences.

Response: We feel that this is precisely why it is so important, as there is a common problem which has not been thoroughly researched, and this study proves that point and aims to alert clinicians of this.

2. When the authors describe implications for future research I would expect the proposal of an investigation on the rate of post-cholecystectomy diarrhoea, predictive factors and implications on QOL conducted by the same authors who came to the conclusions of lack of evidence in the form of a multicentre prospective study rather than a national registry, much more complex to set up.

Response: Further detail has been added to the 'Implications for future research' section of the discussion to incorporate this suggestion (page 12).

Reviewer: 3

Dr. Francesco Mongelli, Lugano Regional Hospital Comments to the Author:
Thank you for the possibility to review the article "Post-Cholecystectomy diarrhoea rate and predictive factors – a systematic review of the literature".
There are some points that need to be addressed before considering for publication.

1.An English review is needed.

Response: The language has been reviewed.

Introduction
2.The actual incidence of PCD is not unknown as the studies included in the present meta-analysis reported it. Authors should mention the reported range of incidence in the literature.

Response: This has been shown in table 1, and added to the introduction (page 3)

3. The aim of the article should be the rate of PCD only (incidence, not the prevalence I guess). Preoperative factors and pathophysiological mechanisms can be reported by a merely descriptive point of view and should not mandatorily be mentioned in study aim.

Response: This has now been corrected (page 4)

4.. I would add a paragraph which include the definition of PCD, timing of onset, resolution of symptoms and therapies in brief.

Response: Unfortunately, there is no standard definition of PCD which is why we have attempted to set up a standardised definition (page 11). Timing of onset is difficult to define as the studies included do not mention this detail, and they also do not mention resolution. Therapies are highly dependent on the cause. If the cause of diarrhoea is due bile acid diarrhoea (BAD) then a bile acid sequestrant may help, however only 63.5% of patients with PCD develop BAD therefore this is not a solution for everyone. This detail has been added to the text (page 4 and 13).

Methods
5. Please indicate the last update of the search (day, month and year when the research has been conducted) Which publication years were considered? No year restriction? That should be mentioned.

Response: This data has been added in the Methods section (page 4).

BMJ Open: first published as 10.1136/bmjopen-2020-046172 on 17 February 2022. Downloaded from http://bmjopen.bmj.com/ on November 5, 2024 by guest. Protected by copyright.

6. Primary and secondary endpoints should be better defined.

Response: This has been clarified in the methods section, page 4.

7. A definition of PCD is mandatory and should include exactly the time range of diarrhea onset after cholecystectomy.

Response: As outlined previously, there is currently no accepted definition for PCD and there is not enough evidence in the literature to include the time range after cholecystectomy as none of the studies included when the diarrhoea started after the cholecystectomy. Therefore, we have tried to propose a definition based on whatever evidence is available, which is on page 11.

8. The sentence "Studies pertaining to persistent symptoms after laparoscopic cholecystectomy, that is symptoms present pre-operatively, rather than new symptoms were also excluded" is unclear.

Response: This means that we specifically looked for studies which investigated *new* symptoms after cholecystectomy, rather than studies which investigated symptoms which were present *prior* to cholecystectomy and then persisted postoperatively.

9. Statistical methods are completely missing.

Response: There were no specific calculations undertaken aside from calculating percentages.

Results:
10. The section "Characteristics of included studies" should provide more details and reports transparently which study reported which outcome.

Response: This data has now been added.

11. The level of evidence of this systematic review should be very low.

Response: This is reported in page 5 'Level of evidence'

12. No information is provided regarding resolution of symptoms. Usually PCD lasts very few weeks, it is very uncommon to have long-lasting symptoms.

Response: The studies that were included did not provide information on resolution of symptoms therefore it could not be reported.

13. It should be useful to report if in the included studies any kind of preoperative antibiotic therapy was administered.

Response: We agree this is important but unfortunately, there was no information in the included studies regarding preoperative antibiotic therapy.

14. I don't understand why pathophysiological mechanisms are included in the results if they can be only reported by a descriptive point of view.

Response: These are not included in the results.

Discussion
15. The reported range of PCD rate among studies is very wide. Do authors have an explanation for that?

BMJ Open: first published as 10.1136/bmjopen-2020-046172 on 17 February 2022. Downloaded from http://bmjopen.bmj.com/ on November 5, 2024 by guest. Protected by copyright.

Response: Yes, This has been added to the discussion (page 12). We felt that the difference between studies in investigative methods and the heavy reliance on patient recall could explain the wide variation in PCD rates

16. Study limitations should be better discussed, in particular, heterogeneity.

Response: This has now been added in a section in the discussion entitled 'Strengths and limitations' (page 12).

17. A paragraph to discuss possible therapies (diet, life-style modifications, etc.) is desired.

Response: A section has been added in the discussion (page 12)

18. Conclusions are not adequate or pertinent with the core content of the article.

Response: There are unfortunately not many conclusions that can be reached considering the paucity of data available. Directions for possible future work are mentioned in the conclusion.

VERSION 2 – REVIEW

REVIEWER	Francesco Mongelli Lugano Regional Hospital, Surgery
REVIEW RETURNED	02-Jun-2021

GENERAL COMMENTS	Authors addressed all comments properly. I find the actual version very informative and interesting.

BMJ Open: first published as 10.1136/bmjopen-2020-046172 on 17 February 2022. Downloaded from http://bmjopen.bmj.com/ on November 5, 2024 by guest. Protected by copyright.