Peer Review File

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Reviewer A

Congratulations on a very well written review of quality of life outcomes for patients undergoing repair of pectus excavatum. A meticulous study, with thorough description of the available literature on the topic.

A couple minor points/suggestions:

1. As the specific QOL survey instruments listed in the review are key to understanding how these data are relevant, would it be possible to include, perhaps in a figure, the actual questionnaires? (unless they are too long to do so). These would be the PEEQ, NQ-mA and SSQ.

Reply 1: The actual questionnaires are not available in the index papers which they were introduced. In these index papers, figures depicting the results of the questionnaire when administered in their papers' respective populations are published. These are inappropriate to include in our paper as they are not the actual questions in the questionnaire. Furthermore, each questionnaire has > 10 questions, making them too long and unsuitable to be placed in a figure. We have addressed this by referencing the papers that these questionnaires originate from, such that any interested parties can contact the respective authors of these questionnaires to obtain a copy.

Changes in the text: See Page 8 Lines 185-186

2. As both pediatric and adult pectus literature was included - was there any difference in QOL outcomes among pediatric and adult patients?

Reply 2: We are unable to analyse this as none of the literature separately analysed pediatric and adult patients. However, we acknowledge that this is a gap in the literature and hope to investigate this eventually.

3. While this study was specific to MIRPE, is there prior data on open repair of pectus excavatum and QOL? Would be helpful to cite, perhaps in the discussion.

Reply 3: We could not find any literature employing the pectus excavatum-specific questionnaires (PEEQ/NQ-mA/SSQ) to compare QOL pre- and post-open repair of pectus excavatum. There are, however, studies comparing QOL outcomes between MIRPE and open repair, but this is beyond the scope of our present study.

Reviewer B

It is still important to underline that psychological aspects are extremely determinant for patients in the choice of surgical therapy. Please allow some comments meant to improve the quality of your paper (see attached pdf file).

Reply 1: We deeply appreciate the reviewer's comments in the attached pdf file and have made the necessary tracked changes in the manuscript.

Reviewer C

Mohamed and colleagues present a systematic review and meta-analysis of quality of life measurements after minimally-invasive pectus excavatum repair. They analysed several databases, had their systematic review registered in PROSPERO and followed the PRISMA-guidelines.

This reviewer has several substantial methodologic concerns:

1. The PRISMA-statement. It is unclear why the authors used an outdated version of the PRISMA-statement. The most recent variant is from the 29th of March 2021, just some months after the authors started their review and just before their completion date.

Reply 1: We thank the reviewer for the insightful comment and have changed to the updated PRISMA 2020 checklist.

Changes in the text: Page 15, Lines 386-387

2. The absolute key component a systematic review is the search strategy and the possibility to reproduce it. Contrary to the PRISMA-statement, which states that the complete search strategy has been reported in the manuscript, it is not. Not even for one database. Likewise, the search date has also not been reported. Consequently, the key components of a systematic review cannot be reproduced and thus render the systematic review useless.

Reply 2: Our team agrees with the reviewer on the importance of providing the complete search strategy and have done so in Figure 1. Searches were conducted from inception date to 23 November 2020.

Changes in the text: Page 4, Line 91

3. Deviations from the study registration are substantial and not reported/clarified. Risk of bias tool: The review registration only describes the use of the Newcastle-Ottawa-Scale, but not the risk of bias tool. Age limit: According to the registration, the study participants were limited to the age of 25 years, but this limit has not been utilized in

the review. Study types: The preregistration also planned the inclusion of retrospective studies and case reports, but this broader criteria have been substantially limited in the report. Time of the postoperative state: The differentiation before and after bar removal has not been pre-specified. Departments: Only thoracic surgery departments were planned to be included, but for example Metzelder et al. is from a pediatric surgical department. Literature search: The authors describe that all searches will be conducted independently by two reviewers, but the review of the full-texts has only been conducted by one reviewer. Choice of the effects method: Only random-effects meta-analyses were prespecified, but fixed effects were used in Figure 3B.

Reply 3: We acknowledge that there have been deviations from the study registration. This is because our team aimed to maximise the number of studies with high quality evidence to be included in the systematic review. We hope to seek the reviewer's understanding that we refined our strategies as the project progressed because we found that it was very limiting if we had stuck to the original conditions pre-specified in PROSPERO. Our team's focus was to produce a sound and comprehensive systematic review. Furthermore, the main outcome of the review was never changed in the process. Our team has edited the manuscript to clarify that we acknowledge these deviations, and adhered to the inclusion and exclusion criteria which were specified in our manuscript.

We would also like to clarify that searches were conducted independently by two reviewers, review of full-texts was conducted by the same two reviewers, while any differences in opinions were resolved by one reviewer who served as an adjudicator. As for the effects method, it was our team's error in using fixed effects but the intention was to conduct random-effects meta-analyses. We have also mentioned in our manuscript that we used the risk of bias tool for the single RCT that was included, on top of the Newcastle-Ottawa-Scale that was initially used for the other studies.

Changes in the text: Page 4 Lines 82-85

4. Risk of bias tool: It remains unclear why a unvalidated tool like the Newcastle-Ottawa-Scale, which has substantial limitations with regard to interobserver-reliability has been used, although a better tool with ROBINS-I is available. The limited knowledge of the underlying instruments is evident from citing reference 13 in support for its use, although Stang discourages it use (and discourages citing him in support for the use of the instrument in DOI: 10.3205/17gmds055).

Reply 4: We appreciate the reviewer's comment on the inappropriate use of the Newcastle-Ottawa-Scale. We have employed the ROBINS-I tool and edited the reference for it accordingly.

Changes in the text: Page 6 Lines 141-144, Table 2 on Page 28

5. It is unclear which effect size has been used. In the methods, the use of the standardised mean difference has been described (line 126), but the results report the mean difference exclusively, although the figures describe the use of the standardized mean difference (Figures 3A and 3B, but see lines 274 and 282-283 to illustrate the confusion of both measurements).

Reply 5: We apologise for the confusion and have since rectified the manuscript to report the standardized mean difference when it is utilized as such in the figures.

Changes in the text: Page 11, Lines 279, 284, 285, 287, 289

6. It remains unclear why studies that report medians and ranges have been excluded although there are methods available to estimate mean and standard deviations (DOI: 10.1186/1471-2288-14-135).

Reply 6: We apologise that it was not clear why medians and ranges were excluded. This has since been clarified in our manuscript. Firstly, results that were reported as medians were likely not normally distributed and thus is not suitable for conversion into means for a meta-analysis. Secondly, although there are methods to estimate mean and standard deviations, not all studies which reported medians provided enough information for such estimations to be conducted. Thirdly, the effects of such estimations on the outcome of the meta analysis is uncertain and hence our team chose to only analyse studies which reported mean and standard deviations to preserve statistical accuracy.

Changes in the text: Page 5, Lines 123-127

7. In Figure 3, the same patients (Kuru et al. n=80) are included up to four times just with different outcomes on different scales, but as these are the same patients, these results can be assumed to be non-independent and thus violate the assumptions of the standardized mean differences used in this analysis.

Reply 7: We thank the reviewer for highlighting this and have re-performed our meta-analysis without any repetition of studies that used the same patient population, whilst choosing the most representative questions for “Self-esteem” and “Extent of interference with social activities”.

Changes in the text: Pages 11-12, Lines 273-291

These substantial methodologic drawbacks render further review rather futile.

Reviewer D

Comments:
1. The title is appropriately constructed and includes reference to the fact that the article is a systematic review and meta-analysis.

2. The running head is appropriate.

Abstract ground: this very clearly states the aim of the article and very clearly delineates the gap in knowledge in the academic world focusing on the area that requires attention, that is the quality-of-life gain following minimally invasive treatment of Pectus Excavatum. The abstract also clearly describes the method of systematic review and meta-analysis. The results have clearly discussed the evidence that is available in the literature, and presenting in a brief results that address the question of the article. This is also well presented in the conclusion.

3. Introduction:
whilst the quality of the introduction is generally satisfactory I believe that there are one or two significant errors of description of surgical technique that have been made. The Ravitch Procedure has been described as a "median sternotomy", this is incorrect, as the statement implies that the breastbone has been divided in half. Clearly this is not the case and the intended statement is a midline vertical thoracic incision. This requires correction.
The description of sternal osteotomy, an extra word or two is required for clarity in the use of this word, e.g. "a transverse external osteotomy".

In paragraph 2, there is correct reference to increased difficulty in exercising, that I can understand as a reviewer, however the words used "a reduction in effort tolerance" does not really provide the reader with an indication of what the effort refers to. This does not give an indication that this is physical effort during exercise required for normal daily activities et cetera this needs to be addressed.

The statement in paragraph 2 commencing "more commonly a surgical repair of PE is performed due to cosmesis…. "Almost negates the question that is being asked in the paper and suggests that surgeons are undertaking cosmetic surgery. If the surgical community were questioned I'm sure there would be a large proportion who disagree with the statement. I believe this statement needs to be modified to represent a belief rather than a statement of truth, as a large body of surgeons will consider that the surgery is undertaken to improve compromised exercise capacity resulting from the defect.

In paragraph 3 of the introduction it says that "this study, we aim to support our hypothesis…" the point of any study is to test a hypothesis rather than to support a hypothesis. The statement suggesting support of a hypothesis suggests bias and this would not be appropriate.

Reply 3: We have altered the manuscript to further precision as per the kind advice of the reviewer.

Changes in the text: Page 3 Lines 54-58, Page 3 Lines 61-62, Line 73

4. The study has been appropriately undertaken and registered as a systematic review with PROSPERO. The registration number has been provided in accordance with guidelines.

The inclusion criteria in the method section appeared to be appropriate in that there is recognition of both paediatric and adult cases of Pectus Excavatum. The study has therefore sought to be inclusive of this group.

Appropriate analysis of articles been undertaken with two reviewers and a third person as an adjudicator in uncertain cases. Quality of data has also been appropriately assessed using the Newcastle-Ottawa scale. Likewise statistical analysis appears to have been appropriate.

Reply 4: We thank the reviewer for the kind comments.

5. The results section is clear with good quality of English describing the breakdown of systematic search findings. And subsequently there has been good description of the analysis of the 20 articles that have been identified and the quality of research undertaken in each.

Assessment of risk bias is also appropriately undertaken, in my opinion appropriate identifying time limits for the quality of analysis, and also correction of data for demographic characteristics. Furthermore limits of apparent randomisation in studies was discussed demonstrating that the compromised nature of the study.

Appropriate discussion of assessment tools for quality-of-life has been undertaken, with an interesting discussion of progression from one questionnaire to another. There is also very good discussion of the variety of the content of questionnaires but there applicability to the subject.

Good detailed discussion of the meta-analysis has been undertaken with explanation for inclusion and exclusion. There has been accurate discussion of a two-stage analysis of the data.

The statistical analysis of the meta-analysis is clearly demonstrated and discussed the benefits on quality-of-life that had been measured in the different studies that have been entered in for analysis. The presentation provides clear description of results with a very clear message of benefit of the procedure.

Reply 5: We thank the reviewer for the kind comments.

6. Discussion

The discussion section is a well-balanced section discussing both the characteristics of Pectus Excavatum its prevalence, and its impact on social and psychological situations, the latter of which is the focus of the paper. The discussion also addresses the role of various questionnaire tools. It then also provides a balanced view on the role of minimally invasive repair of Pectus Excavatum (MIRPE). It also describes the difficulties of the procedure in particular pain.

The limitations of the paper have been well discussed, the limitations of the papers reviewed addressed, and also the complications of statistical statistical bias within any of the reports addressed. There is comment on the need for future studies comments being appropriate.

Reply 6: We thank the reviewer for the kind comments.

7. It is my opinion that this is a well written report of a systematic review and meta-analysis on an important subject. It is my opinion that the information contained in the report is of benefit to the clinical questions being addressed currently amongst groups in both the United Kingdom and across the world in regard to the treatment of Pectus Excavatum.

But for minor changes in the introduction and abstract sections I would suggest that the paper does not require significant review and is suitable for publication.

Reply 7: We thank the reviewer for the kind comments.

Reviewer E

The manuscript is well written and covers a very important subject among an underexposed patient category.

I have the following comments:
• I would recommend the authors to have a native English speaker review their manuscript for grammatical improvements.

Reply 1: We thank the reviewer for the suggestion and have engaged native English speakers to review our manuscript.

• Though psychosocial complaints are often seen in pectus excavatum patients, the deformity most importantly has notable cardiopulmonary consequences. In many

countries, the presence of cardiopulmonary congestion and the deformity's severity dictate surgical correction as these are required for reimbursement. A large part of the PEEQ also focuses on the physical complaints (reported by the patient and parents) which remains underemphasized in the current manuscript.

Reply 2: Our team acknowledges that the cardiopulmonary effects of pectus excavatum are strong indications for surgical repair, and that these are also captured in certain questionnaires. However, as stated in our introduction, the study's aim is to test our hypothesis that MIRPE enhances psychosocial well-being. Therefore, our manuscript did not focus on the physical consequences of pectus excavatum.

• Please remove any duplicate study samples. The study samples from Kuru et al. may overlap since both cited studies were published in 2015 and the NQ-mA was administered. Furthermore, Zuidema et al. administered different questionnaires within one study sample. It is common to include only the most recent study in the meta-analysis of one questionnaire and in the comparison of a theme across different questionnaires.

Reply 3: We note the reviewer's concern and would like to clarify that although Kuru published two studies in 2015 utilising the NQ-mA, only one of the studies was included in the meta-analysis as the other reported medians, instead of means. It is also unclear whether the sample population in both Kuru 2015 studies are the same. Therefore, for the systematic review, we are retaining both studies in order not to miss out on any meaningful observations that can be derived from both studies. As for Zuidema et al, we have revised the meta-analysis to include only the most recent study (2020).

• Although it is not possible to include the PEEQ in the meta-analyses comparing themes across different questionnaires, it would be helpful to provide the results of a meta-analysis on the studies that used the PEEQ for each subdomain within the PEEQ.

Reply 4: We agree with the reviewer that this is a good idea. However, our team would like to share that a meta-analysis solely on the studies that used the PEEQ could not be performed as limited results from the PEEQ were reported (e.g. Kelly 2008 did not report the results from any individual questions / domains, and Gibreel 2016 reported only percentages which could not be used to estimate means and standard deviations for use in a meta-analysis.

• A limitation of the included studies is that they used questionnaires for which a limited number of validated versions are available in terms of language. Linguistic and cross-cultural differences may have influenced the reported outcomes.

Reply 5: We acknowledge that our included studies is limited by language as our team comprises members who are only well-versed in English. We hope to expand our team

in the future to allow for analysis of a larger variety of studies across different languages.