Peer Review File

Article information: https://dx.doi.org/10.21037/apc-21-15

Reviewer A

This is a systematic review of literature focusing on pre-operative factors affecting outcomes following pancreaticoduodenectomy for pancreatic cancer. The authors use the phrase "narrative review" but the article itself is a systematic review. Please modify the style of the manuscript. PRISMA statement is at least necessary.

The title and style of the manuscript has been updated to reflect this. A PRISMA statement and a flow of information diagram (Figure 1) have now been added.

Reviewer B

Dr Russell and co-workers have summarised some preoperative patient and tumour related factors affecting outcome after pancreatoduodenectomy. Although there is little of surprise in this review, I think the authors have gathered recent data in a nice presentation, easy for the reader to assimilate.

I have some comments and questions for the authors, listed as they appear in the manuscript.

Already the title states the authors' intention of a 'narrative review'. This is a concept I'm less familiar with, and maybe others as well. The abstract is somewhat different as it omits results. I see it's in agreement with the narrative review reporting checklist, but I think your paper would benefit with a short comment following the last sentence in introduction, explaining the concept of a narrative review.

After taking on board the comments from all reviewers, the style of the manuscript has been changed to that of a systematic review (and the title changed to reflect this). A PRISMA statement and a flow of information diagram have now been included.

Method

I wonder how you chose the factors you decided to study? Why did you exclude smoking, kidney failure or Ca 19-9? I think the paper would benefit of a wider explanation of the process, including the number of papers you analysed and why you rejected. The review do not cover all studies on preoperative factors and outcome, which is why you need to describe the drop-out. What is the proportion of different studies? (meta-analysis, systemic reviews, single centre studies)

The method section has been expanded to make the inclusion and exclusion criteria clearer. We have only included only variables which will be investigated by the Recurrence After Whipple's (RAW) study (https://clinicaltrials.gov/ct2/show/NCT04596865). We appreciate that there are other important pre-operative factors that we have not mentioned. We have updated the limitations section to reflect this and have made our aims clearer. Figure 1 (flow of information diagram) now illustrates the breakdown of articles. This is also now outlined in the results section.

The different parts are not composed similarly. Some parts present clear data with figures of complications and some just mention if a complication is more or less common if the preoperative factor is present. (for instance; cardiac comorbidity vs diabetes) Can you provide more figures in the parts without?

This has now been corrected. Where available, exact figures have been included so that direct comparisons can be made. Where unavailable, odds ratio/hazard ratio/relative risk has been included to give the reader perspective.

CPET, COPD, MA and SR are abbreviations that needs an explanation first time mentioned. (266, 274, 305, 362)

These have now been added.

The abstract conclusions states malnutrition as non-modifiable, but in the main discussion you comment that it is important to notice sarcopenia to be able to intervene. Please unite your opinion.

To avoid confusion, nutritional status has been removed from the sentence listing potential non-modifiable factors.

Reviewer C

In this manuscript, Drs. Russell and colleagues perform a narrative review of pre-operative factors influencing outcomes following pancreaticoduodenectomy for PDAC. I have numerous comments for the authors to consider.

1. The introduction is very short and succinct, and may benefit from additional background and detail to inform readers about the importance of the work. In addition, as PDAC is recognized to be a systemic disease at diagnosis (even for patients without documented metastases), I believe most providers would agree that systemic therapy is essential to multimodality management, and that margin negative resection is necessary but not sufficient for long-term survival. As such, I think the succinct introduction is a

gross oversimplication of such a complex disease.

We agree that systemic therapy and resection margin status are essential when considering consider survival in PDAC patients who have undergone resection. However, this article solely focuses on pre-operative factors and hence these are not covered. We plan to cover these topics in an additional article (in progress). We have updated the limitations section to highlight that we are only discussing selected variables and have expanded the introduction to make this clear.

2. Similarly, the methods section is also inappropriately short with a paucity of detail. How were the studies evaluated. What studies were included or excluded? Currently this review reads too much as "we did this work, we are reporting these things, and you just need to trust us."

A robust methods section how now been included. This includes details of the search strategy, search results, exclusion criteria, and included papers. A flow of information diagram (figure 1) has also been included so that this is displayed in a succinct format.

3. This review should also include some objective assessment of the quality of the included studies, and the bias inherent in the findings reported. The Newcastle-ottawa scale is one such tool that could be used for this purpose.

Due to the very broad nature of the topics discussed in the article, it is difficult to compare included studies directly. However, as previously mentioned, a robust methods and results section has now been included. This outlines the strict criteria used to identify appropriate articles.

4. How did the authors decide which risk factors would be discussed? Did they decide these a priori, and then find articles to support findings within each category, or did they search for articles and report whatever risk factors were studied? This is unclear - for example, gender is one risk factor discussed, but the authors immediately admit no studies have been performed to assess this risk factor...so why is it one of the factors included? Myosteatosis is another example. This makes me worried that this narrative review is substantially influenced by author bias.

The pre-operative factors in question were all decided on prior to the literature search being carried out. The factors in question will be investigated by the Recurrence After Whipple's (RAW) study (https://clinicaltrials.gov/ct2/show/NCT04596865). This study is ongoing and results are expected in 2022. This has been made clear in the methods and limitations section. We have commented that we are aware that there are other factors which affect outcomes which are not covered in the article.

5. The authors are attempting to discuss both short-term outcomes (post-operative) and long-term outcomes (oncologic), which are 2 very different questions. To haphazardly comment on relationships between both types of outcomes in a few paragraphs is inadequate, and does not do justice to either discussion. This review would be much better served if the authors were more systematic in their approach overall, and they focused on post-operative or oncologic outcomes, but not both.

We agree that we have tried to cover a lot of ground and that this leads to some sections being very concise. However, we wanted to be able to provide readers with a broad overview of the most recent evidence. When identifying candidates for potential surgical resection both surgical and oncologic outcomes are vital so we have included both. We have updated the limitations section to reflect this.

6. The first paragraph of the results should describe the number of studies found, the number excluded (and the reasons why) and the number of final studies included for review. The manuscript also needs a table (a new table 1) that lists the key identifying (reference) information of all included studies, so readers may better understand the studies evaluated, and reference them directly if they so choose.

The results section has been updated to include this. Figure 1 (flow of information diagram) has also been included. We hope this makes this clearer.

7. Similar to above, within each pre-operative risk factor section, the number and types of studies contributing to the narrative review should be reported.

This is now outlined in Figure 1 (flow of information diagram).

8. Similar to above, I don't know if it is appropriate to include preoperative disease stage in this review of pre-operative factors influencing outcomes - of course it influences short and long term outcomes!!! Briefly discussing this in 2 paragraphs of this manuscript seems comically and wholly inadequate. Again, how did authors decide which factors to highlight? This seems to be a highly biased review.

This section has been now altered. No articles which specifically investigate the impact of preoperative disease stage on outcomes were identified. As you point out, one can assume that more advanced stage results in worse outcomes. This section now focusses on pre-operative radiologic tumour characteristics and their impact on outcomes. A non-systematic approach was taken to identify these articles. The methods section has been updated to reflect this.

9. Buried in this review is a 5 paragraph discussion of the relationship between neoadjuvant therapy and outcomes? This is a monumental (and highly controversial, in

the case of resectable disease) topic in itself, and any proper discussion requires consideration of so many nuances (type of therapy, resectability classification, duration, etc.) which are briefly, if at all, discussed in these paragraphs.

We agree that neoadjuvant therapy is a vast and controversial topic. Hence, the section on neoadjuvant therapy takes up about a fifth of the total word count. This is almost twice the length of the next longest section. We have tried to do the topic justice in a short space by summarizing what we feel are the most relevant studies.

10. Is a discussion of pre-operative bilirubin value not inherently tied to a discussion of stunting?

We found that several articles reported that stenting did not necessarily affect serum bilirubin level (surprisingly). Hence the decision to stick with a (very short) section on bilirubin. The format of the article has been altered so that this follows the section on stenting. We hope this means the article now flows better.

11. Limitations section is inadequate, and seems perfunctory.

This section has now been made much more detailed to outline the limitations of the article.