

Peer-Review comments and author responses

Reviewer 1

1. Abstract

-Comment: Please ensure that all relevant information in the abstract is also referenced in the main body of the manuscript (see the comments under Material and Methods). Some information is currently found only in the abstract.

Response: *In agreement with the reviewer, we have changed "This systematic review evaluates" to past tense " This systematic review included". Accordingly, we reviewed missing information in each section of the abstract and added changes to grammar and wording to make the text more concise.*

In the Introduction, the following text was eliminated and added to the introduction's 1st paragraph: "This disease poses a major public health challenge due to its effects on a patient's quality of life, and the significant healthcare costs involved." The second sentence was changed to: "This systematic review aims to offer new insights into understanding the efficacy of acupuncture as an adjunct therapy for this condition".

In the Methods section, changes in the order of the information were added.

In the results, the text "Five RCTs involving participants of Chinese ethnicity were analyzed. Results indicated that acupuncture significantly reduced the frequency of angina attacks and improved the Seattle Angina Questionnaire scores, and pain intensity as measured by the Visual Analogue Scale (VAS)" was eliminated.

In conclusion, the text "Acupuncture could be effective as an adjunctive treatment for refractory angina pectoris. However, limitations of literature reviewed, such as due to the quality of randomized studies, the sample size and generalizability necessitate further studies to corroborate these findings and assess long-term effectiveness" was eliminated.

2. Introduction

-Comment: The introduction states, "Finding high-quality evidence in randomized controlled trials (RCTs), systematic reviews (SRs), and meta-analyses is challenging due to weaknesses in study design, methodology, and small sample sizes (Qi et al.,2022)". Given that this review includes five articles published before 2022, what new insights this review can provide?

Response: *We agree that we weren't clear about the specific analyses that we are offering. We decided to include in the text more explicitly that the analysis is about refractory angina and that is the difference between previous reviews.*

The revised text reads as follows: "This review aims to contribute to understanding the effectiveness of acupuncture as a complementary therapy to standard medication for the specific context of RAP refractory angina as defined by the 2019 ESC Angina Guidelines, which prior reviews have not done."

-Comment: Several sections currently placed in the Discussion should be included in the Introduction (see comments for Material and Methods and Discussion).

Response: We agree with the reviewer that in the Discussion section there was similar information to the Introduction and the first paragraph of the Introduction has been rewritten to include this information and in the Discussion section the first 3 paragraphs have been eliminated. Changes to the Discussion section have been added for a more cohesive explanation.

3. Materials and methods

-Comment: Please organize the information more clearly. I recommend using bullet points for categorization.

Response: *As suggested by the reviewer, the manuscript text has been assessed for grammar and wording as to have a more cohesive text. Numbering was added to the Inclusion and Exclusion Criteria section for a more organized explanation of this section based on the sample that the reviewer provided*

-Comment: Regarding the outcomes, the primary outcome was not prespecified, yet four outcome measures are listed under eligibility criteria. In section 6.4.1, angina attack frequency is identified as the primary outcome. The primary outcome should be clearly defined in the Material and Methods along with its rationale.

Response: *Thank you for the feedback. We made sure that the primary outcome was clearly mentioned at the beginning of the "Materials and Methods" section. We added a paragraph on the rationale: "Our rationale for the choice of frequency of angina attacks as the primary outcome is that this has been found to be related to future hospitalization, revascularization, and death, independently of other clinical risk factors. (Beatty et al., 2014.)."*

-Comment: Target Study design is unclear in the Material and Methods, although it is noted in the abstract and table 2 that only RCTs were selected.

- 1) What type of articles are considered to have "incomplete data"?
- 2) If you are focusing solely on RCTs, it should be explicitly stated in the criteria.
- 3) Are meta-analysis and systematic reviews included or excluded from the analysis?
- 4) The inclusion criteria should be organised more systematically. The current description mixes the criteria for both study inclusion for review and participant inclusion for each study.

Response: Dear reviewer, after reading your comments we agree that the wording can be improved to avoid confusion and to specify the proposed points, so below I list the way in which we address each point indicated

1) With inaccurate or incomplete data on the characteristics of the PICOTT.

2) We have specified in the criteria that we only include randomized clinical trials.

3) We have specified that meta-analyses or systematic reviews are excluded, focusing solely on controlled clinical trials.

4) We have made an adjustment in the wording to avoid confusion, separating the inclusion criteria for the studies as well as the inclusion criteria for the participants.

-Comment: Regarding inaccurate data or incomplete data, what do the authors mean by this? Please clarify.

Regarding exclusion criteria, the authors must ensure all criteria should be denied in each paper. Could the authors confirm that all included studies have execution criteria for pregnancy? It might be only written in the original study protocol.

Response: We reviewed in depth and agreed to remove the pregnancy exclusion criterion, as there was one article that did not explicitly mention this point. Also, we agreed that the phrase inaccurate or incomplete data can be confusing, so we have rewritten the information and specified what we mean, Randomized controlled trials inaccurate to our PICOT.

-Comment: Please specify the publishing year range for the search in the Material and Methods. In the abstract, the authors mentioned “randomized controlled trials (RCTs) published up to July 13, 2024”, but there is no corresponding description in the Material and Methods.

Response: We agree that we weren't clear in both sections about when the final search was done. We addressed changing in both sections that the final search was until July 13, 2024.

The revised text reads as follows on pages 2 and 5:

In the abstract: “The final search was performed on July 13, 2024.”.

In Materials and Methods: “The final search was performed on July 13, 2024, and papers published up to this date were included (Table 2).”

-Comment: Did you prespecify the primary outcome? It appears in the Results (and in the abstract), but there is no mention of it in the Material and Methods section.

Response: We have reviewed and saw that it was missing so to make it clearer we added outcomes in a PICOTT format. The new text reads as follows:

This systematic review adhered to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) 2020 guidelines. The study design was based on the following PICOTT framework: (P) Adults with RAP; (I) Acupuncture plus standard therapy; (C) Standard therapy alone; (O) primary outcome: frequency of angina attacks, secondary outcomes: use of

nitroglycerin, Pain reduction and quality of life; (T) No time restrictions; (T) Randomized controlled trials.

-Comment: In section 5.4, the authors state, “Groups of 4-9 people, arranged alphabetically, were formed to reach a consensus on the extracted information”. Does this mean that the task of developing the search strategy was assigned to a few authors? If so, please specify the name of the author(s) responsible for strategy development. I recommend creating a section for author contributions to detail each author's role.

Response: Each article was reviewed by two independent reviewers. Any discrepancies or uncertainties regarding study eligibility were resolved by a third reviewer. We removed the part of groups of 4-9 people as we agree with you that it is ambiguous

-Comment: Section 5.X should focus on methodology. However, some results are currently included in the Material and Methods. For example, “we included three articles in English and two in Chinese” should be in the Results.

Response: *We are agreed that the sentence should be included in results and changed it accordingly*

-Comment: The authors initially said in the Results that there were five articles, three in English and two in Chinese, but in the end, five Chinese papers were extracted for analysis. Could you please clarify this difference?

Response: *Following the suggestion we have clarified that there were 5 articles that were finally included in our systematic review, of these 5 clinical trials, all 5 were conducted with the Chinese population, however 3 were written in English, and two in Chinese, which were translated.*

-Comment: Please confirm the studies published solely in Chinese were properly registered to a public registry, such as ClinicalTrials.gov. How do you assess the quality of the journal if it is only written in Chinese and the publication policy is addressed only in Chinese? Did you confirm they are peer-reviewed or grey journals? It would be better to explain in the Material and Methods how you can assess these issues.

Response: *Following the suggestion we have ensured that the articles written in Chinese were properly registered in public records of China and were also published in peer-reviewed journals. We specify in our limitations that details of the peer review process or quality assurance of the journals could not be assessed, although they were published in peer-reviewed journals.*

-Comment: A review paper needs a clear methodology for data analysis. Since this is not a metanalysis, the authors should describe the descriptive analysis that they used.

Response: We agree and have now clearly described in the data synthesis section how we analyzed the information and the tools we used.

-Comment: How was heterogeneity assessed? This should also be detailed in the Material and Methods.

Response: *We could not assess heterogeneity as a meta-analysis was not performed but we have now clearly described in the methods how we expected heterogeneity and stated why we did not expect to perform a Meta-analysis*

4. Results

-Comment: The authors mention having 8 Chinese articles, 2 of which were not retrieved, and 5 translated. What happened to the other article? Additionally, the final analysis includes 5 articles—is this the same set as the 5 that were translated?

Response: *Thank you for pointing out this mismatch. We have clarified the selection and retrieval of the articles in the results section. We explicitly state that the final analysis includes five articles (3 in English and 2 translated from Chinese). The discrepancy of numbers has been resolved.*

-Comment: In the Results section, the authors stated that 304 articles were excluded by eligibility. However, the criterion of relevance is not clearly mentioned in the exclusion criteria, which only references "inaccurate/incomplete data". How was relevance to the research question assessed?

Response: *We have clarified that "inaccurate/incomplete data" referred to RCTs with incomplete data regarding characteristics stated in our PICOTT*

-Comment: Figure 1 does not show the articles that could not be retrieved, which are mentioned in the text. I wonder if they are included in the 304 articles. The large number of exclusions should be clarified in line with the previous comment.

Response: *Figure 1 was corrected including the not retrieved articles*

-Comment: In the file of "Table 1", all tables and figures are included, but they were also submitted separately. The authors may delete all tables and figures from "Table 1" except Table 1 itself and arrange all tables and figures according to the author's guidance.

Response: *Thank you for pointing out this mistake and we have procured that all tables be submitted separately*

-Comment: In Table2, "Cochran" is used, while "CENTRAL" is mentioned in the manuscript. Please ensure consistent terminology throughout the document.

Response: *We agree with the inconsistency and have decided to keep CENTRAL throughout all the manuscript and tables*

-Comment: The reference needs to be specified more clearly in the body of the manuscript, as multiple references have the same name and publication year. It is difficult to identify the 5 analyzed papers from the references provided.

Response: *We agree that we had a problem with the references as there are 3 Wang references. Following the APA format we specified the initials of each Wang author. These were found in Chinese-language peer-reviewed journals and were publicly registered (Deng et al., 2018; Huang et al., 2021; M. Wang et al., 2015; Zhang et al., 2019; Zhao et al., 2019). // There were 3 Wangs in the references, our article is M. Wang*

-Comment: Please change the font style from italic bold to normal to normal in Table3, unless there is a specific reason behind this formatting.

Response: *Thank you for pointing this out and we agree with the suggested changes. The font style in Table 3 was changed from italic bold to normal as there was no particular reason for this format.*

-Comment: The last sentence of section 6.2 should be deleted: Outcomes assessed the frequency of angina attacks, nitroglycerin usage, the Seattle Angina Questionnaire, and pain severity, unless the authors intend to summarize how many articles contain the primary information. This is explained in section 6.4.

Response: We agree with the suggestion and removed this sentence from the description of population in the results

-Comment: If this manuscript is a systematic review, the data should be assessed, at least, for the primary outcome. In the Results, the authors stated how many articles have this endpoint and how many showed statistical differences. However, each article has different observational periods, making it unclear how much effects were observed and their clinical relevance. Without this information, it is difficult to understand why the results are considered positive.

Response: *Due to a large amount of heterogeneity between trial designs, we decided to not perform a meta-analysis of the primary outcome, because of which we cannot provide a number / effect size to support our assertion regarding the primary outcome. That said, three of the five studies find (at similar observational periods) that the primary outcome was statistically significant. One study that does NOT find significance reported this outcome as part of the Seattle Angina Questionnaire, from which numbers for angina attack rate had to be extrapolated. In addition, baseline angina attack rates were significantly lower for this study than for the ones that showed positive outcomes, possibly contributing to negative findings due to issues with power. One study did not report on angina attack rates as an outcome. We have included these clarifications in our text, and highlight specific suggestions for future research to address these gaps.*

-Comment: Regarding the secondary outcome, some showed statistical significance (2-3 articles), while others did not. How do you assess the effectiveness? Do you address these are not significant? How can the reader translate these findings into practice?

Response: *For nitroglycerin usage : to clarify effectiveness / translate into practice, we're trying to say that frequency of use decreases, but dosage does not - based on different RCTs answering slightly different questions. In addition, we accept that we cannot provide definitive answers for some of the secondary questions. We list areas that need further research before conclusions can be drawn. The paragraph in question was thus changed to the following:*

Four studies measured the use of nitroglycerin as rescue medication. Of these, a statistically significant decrease in the frequency of nitroglycerin usage for the intervention group was found in two studies (M. Wang et al., 2015; Zhang et al., 2019). Two other studies (Huang et al., 2021; Zhao et al., 2019) found no differences in the dosage of nitroglycerine used as rescue medication between control and intervention groups. Three studies measured pain intensity as an outcome. Of these, two (M. Wang et al., 2015; Zhao et al., 2019) found a significant reduction in pain intensity, as measured by the Visual Analog Scale, for the intervention groups. One study (Zhang et al., 2019) found a decrease in pain intensity for all groups, and the difference between the intervention and control groups was not statistically significant. Considering the limitations of the included research literature, it is still necessary to conduct further high-quality RCTs to assess the effect of acupuncture on pain severity and rescue medication usage for those with refractory angina pectoris.

-Comment: What is the conclusion regarding the Risk of Bias (ROB)? Do the authors consider 5 articles have acceptable quality to discuss the data, especially given that 2 of 5 were classified as high risk of bias.

Response: *We accept in our limitations section that 1. Due to the nature of intervention (acupuncture or sham acupuncture performed by an acupuncturist), inherent unblinding of the acupuncturist and resulting bias will occur for ANY acupuncture trial. 2. Trials analyzed also had other issues (selective reporting, in one case only for a secondary outcome).*

Even with these limitations, we find it acceptable to include these 5 articles in our review. Text was changed to clarify this intent. The inherent unblinding of the acupuncturists, and selective reporting of secondary outcomes not pertinent to our review that resulted in the judgment of a high risk of bias were judged to not detract significantly from the quality of our review.

5. Discussion

-Comment: The first paragraph of the Introduction should be relocated and integrated with the existing sections. Instead, the authors could provide a summary of the findings in the opening paragraph of the Discussion. Also, consider replacing the paragraph with the one with more specific data.

Response: *Thank you for pointing this out. We have changed the first paragraph of the Introduction to: "Angina pectoris (AP) is a common manifestation of coronary artery disease*

(CAD). CLARIFY study, reports as a quarter of CAD patients, and most cases resolve with treatment within a year. In 2019, the European Society of Cardiology (ESC) defined refractory angina pectoris (RAP) as chronic angina persisting for more than three months despite escalating medical therapy to second and third-line treatments (Davies et al., 2021). Presenting in 5-15% with AP, and portends higher cardiovascular risk for patients (Chen et al., 2023; Mesnier et al., 2021). With an aging population, the epidemiological characteristics may be evolving, posing a major public health challenge due to its effects on loss of quality-adjusted life years (QALYs), diminished life expectancy, and the significant healthcare costs involved (Gallone et al., 2019; Knuuti et al., 2020). Associated with substantial morbidity, frequent hospitalizations, treatment adjustments, and diagnostic procedures, which escalate healthcare resource utilization and contribute to elevated levels of depression and anxiety (Fortunato et al., 2024; Gallone et al., 2019). The current treatment for RAP refractory angina primarily involves standard pharmacological therapy, and alternative therapies are emerging (Knuuti et al., 2020)."

In the second paragraph of the Introduction, the phrase "and fewer adverse effects" was eliminated. In the third paragraph, the phrase "refractory angina attacks" was replaced by "chronic stable angina".

The third and fourth paragraphs of the Introduction were combined to make 1 paragraph. From the fourth paragraph only the sentence "Finding high-quality evidence in randomized controlled trials (RCTs), systematic reviews (SRs), and meta-analyses is challenging due to weaknesses in study design, methodology, and small sample sizes (Qi et al., 2022)" was included and the sentence "This review aims to contribute to understanding the effectiveness of acupuncture for refractory angina by synthesizing evidence from RCTs, focusing specifically on the context defined by the 2019 ESC angina Guidelines", was changed to "This review aims to contribute to understanding the effectiveness of acupuncture as a complementary therapy to standard medication for the specific context of RAP".

-Comment: The second paragraph still reads like an introduction. It may be more effective to state “the importance of this review is XXXXXXX, considering the limitations of other papers (and this gap can be highlighted in the Introduction) • • • •”. Alternatively, you could use the sentence later you used; “This review is the first to specifically address acupuncture for refractory angina, with patients receiving standardized medical treatment based on chronic stable angina guidelines. It also encompasses various acupuncture modalities, broadening the therapeutic scope”.

Response: *We totally agree with your suggestion. and integrated this recommendation to the next recommendation to make a new paragraph to start the discussion*

-Comment: The third paragraph of the Discussion largely repeats content from the end of the Introduction, except for the last sentence which moved to the beginning of the Discussion to provide a summary of your findings.

Response: *As stated previously we agree with this suggestion and the one previously made and integrated the the sentences you recommended to keep and made a new first paragraph of our discussion that was more specific about the findings.*

-Comment: Most of the content in paragraphs 4-6 should be integrated to the Result.

Response: *Yes we totally agree and eliminated this text from the discussion*

-Comment: In the Discussion, the author mentioned that “this systematic review has several strengths. All included studies were randomized controlled trials, the gold standard for establishing effectiveness (Hariton & Locascio, 2018). “- While it is true, it may not be feasible to discuss the effectiveness even with RCTs under a strictly controlled setting. Each manuscript you extracted seems not to be designed as a confirmatory trial. Could the authors discuss the effectiveness of this review in this context?

Response: We agree and based on your recommendation removed having RCT's as a strength and instead we presented the strengths from our inclusion criteria and how our results can be applied to real world patients and this being the effectiveness of our review.

-Comment: In the 8th sentence, there is a description; “This review indicates that acupuncture could effectively reduce angina attack frequency and improve the quality of life in patients with refractory angina pectoris”, but It is unclear which data supports this conclusion. Was this based on three of five significant studies related to angina frequency and quality of life? On the other hand, two of five on nitric oxide (NO) and one on pain are not considered positive. To draw a conclusion from a small amount of data without meta-analysis, study quality should be carefully discussed.

Response: *Thank you for pointing this out. We decided to clarify the findings by specifying the articles that provided this information to explain how these studies suggest improvements in pain intensity and quality of life.*

New text: The conclusion that acupuncture can reduce angina attack frequency and improve quality of life is primarily supported by three studies (Huang et al., 2021; M. Wang et al., 2015; Zhao et al., 2019). These studies showed statistically significant reductions in angina attack frequency and improvement in quality of life. However, two other studies (Deng et al., 2018; Zhang et al., 2019) focusing on nitric oxide and pain intensity did not yield significant results. Therefore, the overall evidence remains limited by the small sample size and heterogeneity of the interventions.

-Comment: Add comments on the quality of articles in the limitation section (see comment 3 for Material and Methods). Since readers cannot replicate the results without translation, they do not have a clue how to critically assess them.

Response: *Thank you for your suggestion. We have expanded the limitations section in the discussion and included an assessment of the quality of each included study. We have also added the replication challenge due to language barrier*

-Comment: Please include a discussion of the quality of the articles in the limitations section. Since readers cannot replicate the results without translation, you should explain this issue clearly if you intend to publish this paper.

Response: *We agree and have discussed the quality of the articles in the limitation section and acknowledged the limitations in reproducibility due to translation*

New Text: Key methodological issues included blinding, intervention reliability, and generalizability. All studies except Huang et al. (2021) included a control group that received only standard medication and, therefore, was unblinded, increasing the risk of response bias for subjective outcomes (Hróbjartsson et al., 2011). Only Zhao et al. (2019) and Huang et al. (2021) specified licensed acupuncturists, raising questions about intervention reliability. Additionally, the short trial durations limited the ability to assess long-term efficacy. Despite these concerns, these trials are judged to be of sufficient quality to include in our review, given that acupuncture as an intervention necessitates unblinding of the acupuncturist, and there is no evidence suggesting the effectiveness of blinding in this situation (Trinh, 2003).

Additionally, these were the best trials that met the criteria for our research question. Generalizability is also limited as all studies were conducted in China, potentially affecting applicability to other ethnic groups and regions. Factors like participant expectations, regional differences in acupuncture practices, and patient characteristics can influence outcomes (Cao et al., 2020; Linde et al., 2007; Mao et al., 2010). Additionally, the fact that two of the articles were originally in Chinese and required translation may compromise the reproducibility of this review for non-Chinese investigators.

-Comment: Provide an explanation for the limited use of acupuncture in other countries. The authors concluded that it is employed as a complementary approach to standard care. The discussion does not currently address present standard supportive care. How does this compare with the current use of complementary care alongside standard care in other countries? I could not see the discussion around present standard supportive care. Additionally, is there any variance across the countries in this aspect?

Response: *Thank you for your valuable suggestion. We provided a more detailed explanation regarding the limitations and variance of acupuncture in Western countries compared to China, as well as its role as a complementary treatment for refractory angina pectoris.*

-Comment: Safety data was not assessed but discussed in the Discussion. If the authors wish to claim that acupuncture has negligible risk, they should assess the safety profile of this technique reported in each article. It is unclear whether this discussion is based on the author's opinion, or the data presented.

Response: *Thank you for this important suggestion. We completely agree and have included a paragraph in section 6.6, "Main Results and Heterogeneity," where we explain the safety outcomes of the studies included. We have also added a part on safety on the discussion to complement these findings*

-Comment: It would be beneficial to offer authors perspectives on how to overcome the challenges associated with study design in this field. Otherwise, readers do not gain much new insight from the current discussion, particularly considering the publication like Qi et al. (2022)

Response: We have reviewed the publication by Qi et al. (2022) and based on this systematic review we believe our systematic review does give more insight as we included specifically refractory angina pectoris, a weakness Qi et al. (2022) pointed out on previous reviews that did not specify based on subtype of angina pectoris. We have also included stricter inclusion criteria such as only including RCT's where participants all received standard therapy for chronic stable angina.

6. Conclusion

-Comment: Again, it is not clear to me how the authors reached this conclusion.

Response: *We acknowledge that there could be confusion so we rewrote the conclusion so it is clear that our conclusions are not conclusive due to the limited articles we included and only a suggestion and further studies are necessary*

-Comment: Remove "could" and provide a clearer, more definitive statement in the Conclusion, I think there is a difference between stating your conclusion clearly and acknowledging the need for additional evidence.

Response: *We agree and removed could from the conclusion and acknowledged the need for additional evidence*

7. Others

-Comment: Regarding authorship, is it possible to have more than five first authors in the PPCR? Typically, two authors might be listed as having 'these authors contributed equally', but listing too many authors as first authors is not generally recognised as appropriate. The first authors should be chosen carefully according to the International Society for Education's definition (ICMJE). With so many first authors, I wonder who is, in fact, responsible for them.

Response: We acknowledge the confusion and lack of transparency so authorship was revised and there are now 6 first authors instead of 10 and a section called disclosure about authorship was added

-Comment: What is the role of three senior authors? Different two authors are listed as corresponding authors. Please specify their roles and responsibilities.

Response: We agree that with more than one senior author and corresponding author there is a lack of transparency in roles and responsibility so 1 senior author and 1 corresponding author were maintained

-Comment: Given the above circumstances, the authorship and their contributions are unclear. This ambiguity is not advisable from a conflict-of-interest perspective. I recommend that the contributions of each author be clearly explained.

Response: We agree on the previous confusion in authorship due to which we revised authorship and a section of disclosure was added. Therefore we believe that the individual contributions of each author won't be necessary

-Comment: Ethical considerations, registry information, budget, and conflict-of-interest should be mentioned even if it is a review.

Response: Thank you for this insight and following your recommendation a section called disclosure was added that addressed these issues and the protocol was disclosed in the material section

-Comment: Please ensure that all tables and figures are referenced within the manuscript. Currently, not all figures and tables are mentioned

Response: Thank you for your correction, we have now included all of the references of the tables and figures we include in our systematic review

-Comment: Complete all figures and check the document's integrity. Some figures do not include necessary numbers, such as others (n=) in Figure 1

Response: We agree and have now double checked all of the figures in order for them to be coherent, paying special attention to the ones that do not necessarily include numbers

-Comment: There is inconsistency in the documents, likely due to multiple authors contributing to its development. If the document is too difficult to read due to its inconsistency, it may be rejected by the editors.

Response: Thank you for your feedback. We have carefully reviewed the entire manuscript to ensure consistency in style and terminology. Sections written by different authors were harmonized, and we believe these revisions have enhanced the clarity of our systematic review.

Reviewer 2

1. Abstract

-Comment: It is recommended to expand the results section to include the findings described in the manuscript.

Response: Thank you for the feedback. We agreed and expanded the results sections, including what we found in the secondary outcomes.

2. Introduction

-Comment: The only recommendation is to try to make it more concise as it is a bit lengthy, and there are long paragraphs that are not supported by the literature.

Response: We agree that information that was included in the Introduction could be found in other sections of the text like the Material and Methods and Discussion, making it long and repetitive. Changes suggested have been added, especially for the first paragraph which had similar information to the first paragraphs in the Discussion section.

-Comment: Throughout the manuscript, the evaluated outcomes are mentioned, which were several including frequency of attacks and use of nitroglycerin, but only two are mentioned in the PICOTT. Please clarify

Response: We agree that not all the secondary outcomes were included in the PICOTT, so we specified all the secondary outcomes.

The revised text reads as follows: "The study design was based on the following PICOTT framework: (P) Adults with RAP; (I) Acupuncture plus standard therapy; (C) Standard therapy alone; (O) primary outcome: frequency of angina attacks, secondary outcomes: use of nitroglycerin, Pain reduction and quality of life; (T) No time restrictions; (T) Randomized controlled trials."

-Comment: Regarding the results, it would be beneficial for better understanding of the manuscript to create a table displaying the obtained findings, as it would allow for comparison of the analyzed studies and a clearer understanding of how the conclusions were reached.

Response: Thank you, we have provided the detailed results in our table 3.

Reviewer 3

-Comment: Thank you so much for saying you would accept our initial submission. We have revised it based on all the reviewers recommendations including your own and hope that you will still accept the new cleaned manuscript. I suggest you relate the findings to previous systematic reviews or meta-analyses on acupuncture in angina pectoris, even if it's not refractory

Response: We agree and clarified in our discussion that these results are similar to previous studies that specifically used patients with chronic stable angina as a population and not refractory angina pectoris.

-Comment: It would be a great idea to check if the studies included an evaluation or screening for mental health, since these can influence a person's perception of pain.

Response: *We agree that this would be very interesting to study but sadly only 1 paper by Wang et al. (2020) included this outcome and used self-reported scales when blinding was an issue. Therefore, we deemed it not adequate to report these results*

Reviewer 4

1. Methods

-Comment: I have no further comments regarding the methodology; however, I am worried that the assessment of angina pectoris improvement can be heavily biased by the natural unblinding of the intervention (acupuncture).

Response: *We agree that blinding may be an issue. For our review, we only included those studies that compared acupuncture with sham acupuncture, or another modality of acupuncture. This was done to ensure that participants remain blinded to their group, even if those providing the acupuncture necessarily have to be unblinded. That said, we highlighted those trials that were at a high risk of bias due to issues with blinding. This was compounded by the fact that one of these trials that had possibly unblinded participants reported on patient-reported outcomes, contributing to these trials being judged as being at High risk of bias. Additionally, other systematic reviews looking at acupuncture as an intervention make the same admissions regarding high risk of bias, a practice we judge promotes transparency.*

-Comment: I totally agree with the difference between acupuncture techniques in the included studies. Although the same acupoints were addressed, the relative effectiveness between techniques is unclear.

Response: Relative effectiveness between techniques was directly addressed in Huang, which compared high sensitivity vs low sensitivity groups. Outside of this study, since there is not clear consensus on which specific acupuncture technique is effective, we have assessed the effectiveness of acupuncture as a whole. This has been the practice that other systematic reviews about acupuncture have also done

-Comment: Lastly, I would like to question the criteria for refractory angina pectoris. How was this addressed in the studies included?

Response: We acknowledge the lack of clarity in this matter. In our systematic review refractory angina pectoris was defined as chronic angina persisting for more than three months despite escalating medical therapy to second and third-line treatments by the European society of Cardiology in 2019. (Davies et al., 2021). To be included in our review all studies had to include patients diagnosed with stable angina pectoris according to the American College of Cardiology/American Heart association or the Canadian Cardiovascular Society, with a duration of at least three months which we have described in our Inclusion and Exclusion criteria section.

Because the criteria of refractory angina is recent we have checked the inclusion and exclusion criteria of all included studies to guarantee that they have met this definition.