

Peer Review File

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Review Comments (Round 1)

Reviewer A

This is a well-written manuscript.

Only one typo that needs to be corrected. In the line 101, "PND" should be "PNA".

Reply 1: we would like to thank reviewer 1 for his time and comment, we changed it in the text by replacing PND with PNA, check line 104.

Reviewer B

Mahmoud et al. performed an updated meta-analysis on 15 RCTs and showed that PCD is superior compared to PNA in terms of success rate, recurrence and time to achieve 50% reduction. Length of stay is comparable.

This is a timely meta-analysis since the last meta-analysis in 2015 on 5 RCTs by Cai et al. Good methodology was described by the authors and risk of bias assessment is adequate. Sensitivity analysis was also performed to explore heterogeneity. I do not have any concerns with the statistical analyses.

However there are a few major and minor points which i would like to raise as stated below. In view of these points, i would recommend a major revision prior to acceptance of the paper. Our institution has also performed extensive research on pyogenic liver abscess and would recommend including these points for discussion as stated in the respective points below.

major points

- general comments: overall use of grammar and sentence structure is poor which makes reading difficult. i would recommend for the whole manuscript to be edited by English proofreading services.

Reply 1: Thank you so much for your feedback. We reviewed and improved the grammar and sentence structure as instructed.

Change in the text; check lines 66, 67, 71, 72, 75, 77, 83, 84, 85, 86, 93, 99, 106, 137, 174,175, 179, 188, 189

- results: data on microbiology is lacking.

Reply 2: Thank you very much for your suggestion. We added table 2B illustrating the microbiological diagnosis

- results: it is mentioned there is male predominance and right lobe was more affected. how about for PCD group vs PNA group? how about incidence of solitary vs multiple abscess, and multiloculated abscess, and size of abscess? it is important to include radiological findings as these are factors which have been shown to predict failure of PNA / PCD.

Reply 3: Thank you very much for your suggestion, but we have already clarified the radiological findings in Table 2 A (baseline characteristics). Also, we added the abscess size in Table 2 (study characteristics).

- results: what is defined as success rate? i think various studies would have different definitions. e.g. technical success, where there is confirmed clearance of abscess, or clinical success, where patients improve clinically as shown by clinical status, vitals, biochemistry markers and/or radiological findings? i think this is important for interpretation

Reply 4: Thank you very much for your suggestion. We edited Table 1 accordingly adding the definition of success rate for each RCT, we also gave a brief definition in the text

Changes in the text, “clinical resolution of infection and radiological evidence of abscess resolution, either total disappearance or more than 50% decrease in the longest diameter before intervention for detailed definition check Table 1” line 126 : 128 and 130: 131

- results: how about failure requiring surgical intervention? mortality? i noted discussion mentioned that Yu et al described 5 deaths, but this is not described in results on in-hospital / 30-day mortality.

Reply 5; thank you for pointing this out, we handled these points by giving detailed information about the failure rate and the fate of the patients who did not achieve resolution for each study

Changes in the text; check line 198: 230.

- discussion: good discussion on success rate. however, discussion is lacking on a few points:

(1) demographics - it is likely demographics will be similar since only RCTs were included. however, important factors such as presence of diabetes and underlying biliary disease should be discussed. strong evidence has shown that DM is associated with worse mortality.

Reply 6; Thank you for the information, we cited 2 papers discussing this point and discussed it

Change in the text; “Morbidity and mortality are highly affected by several factors such as the presence of diabetes, which is accredited to low immunity, biliary disease, and type of organism, a recently published meta-analysis concluded that showed that klebsiella pneumoniae has lower mortality than non- klebsiella pneumoniae pyogenic liver abscess” line 318: 322

(2) radiological findings - e.g. size, presence of multi-loculation and presence of gas formation? there should be a focus on discussion on the size of abscess as well, as cut-offs have been used for size of abscess. cut-off of 4cm has been used in several studies to determine need for PCD. [Cite: Chan, K.S., Shelat, V. (2022). Pyogenic Liver Abscess. In: , et al. The IASGO Textbook of Multi-Disciplinary Management of Hepato-Pancreato-Biliary Diseases. Springer, Singapore. https://doi.org/10.1007/978-981-19-0063-1_66] I think this point needs to be discussed, and whether there is any size difference for PNA and PCD. There also needs to be small mention on why size is important - because of the volume of a sphere [Cite: Shelat VG, Chia CLK, Yeo CSW, Qiao W, Woon W, Junnarkar SP. Pyogenic liver abscess: does Escherichia coli cause more adverse outcomes than klebsiella pneumoniae? World J Surg. 2015;39(10):2535–42]

Reply 7; Thank you for the notes, we did as suggested, cited the papers, and changed the manuscript accordingly, check lines 336:354

Change in the text; “Radiology plays a key role in determining the prognosis of pyogenic liver abscess (46, 47), gas formation was shown to be associated with higher mortality (48, 49), multiple loculi within

the abscess, and increased size of the abscess were all predictors for percutaneous drainage failure (50, 51).

The size of the abscess is a decisive factor for the prognosis and the intervention plan(51-54). It is more likely for larger abscesses to rupture, causing infection to spread in the peritoneal cavity which may end up causing sepsis increasing morbidity and mortality, thus large and giant-sized abscesses may need prompt surgical intervention, but stratifying the intervention based on the size of the abscess is vague in the literature with no consensus on when exactly to choose surgical intervention over percutaneous drainage (51-54).

a study by Shelat et al. suggested that an abscess of four cm or larger is the cut-off value for the need for PCD (54) , and there is no consensus that an abscess larger than 10 cm is a strict indication for surgical intervention. However, surgical intervention is considered the favored intervention for patients with accompanied intraperitoneal pathology such as acute cholecystitis to allow cholecystectomy and drainage with the only absolute indication for surgery is rupture (51, 55).

Although abscess size is a key role for the success rates, the clinical resolution, and which method to be used for drainage, it is not the only factor, as multiloculation, gas formation, and virulence of the causative organisms need to be implicated in the decision (51).”

(3) microbiological findings. we recently performed a meta-analysis on klebsiella pneumoniae (KP) vs non-klebsiella pneumoniae pyogenic liver abscess (PLA) and showed that KPPLA has lower mortality than non-KPPLA. This point should be discussed [Cite: Chan, K.S.; Chia, C.T.W.; Shelat, V.G. Demographics, radiological findings, and clinical outcomes of Klebsiella pneumonia vs non-Klebsiella pneumoniae pyogenic liver abscess: a systematic review and meta-analysis with trial sequential analysis. Pathogens 2022]

Reply 8; Thank you for the information, we cited the paper and changed the text accordingly

Change in the text; “Morbidity and mortality are highly affected by several factors such as the presence of diabetes, which is accredited to low immunity, biliary disease, and type of organism, a recently published meta-analysis concluded that showed that klebsiella pneumoniae has lower mortality than non- klebsiella pneumoniae pyogenic liver abscess”

(4) good that you mentioned difficulty with PCD include nursing care. length of stay (LOS) was described to be similar between PCD and PNA due to increased nursing demands. however, with better drainage and reduced duration of antibiotics, this should theoretically result in shorter LOS. Is there any other reason for this?

Reply 9; thank you for the comment, we think that thick pus can be another factor that led to this and also multiloculation. We cited 2 papers that supported this.

Changes in the text; “thick pus which is not easy to be drained percutaneously, and multiple loculi within the abscess, which is a well-established element in PCD failure, despite its faster resolution results”

minor points

abstract

for continuous outcomes, please include units. i assume those are measured in days.

Reply 1; thank you for your comment, we changed the abstract accordingly

Changes in the text: we added “The results were heterogeneous for all the continuous outcomes which were all measured in days”

Introduction

- line 64-65: the most common type of bacterial pyogenic abscess is Klebsiella pneumonia, followed by Escherichia coli. Not Staphylococcus aureus

Reply 2: thank you for the correction, we changed the text accordingly

Changes in the text; “The most common type of liver abscess is bacterial, with Klebsiella pneumonia Staphylococcus aureus and Escherichia coli as the primary pathogenic micro-organisms”

- line 82: please use full form first i.e. ultrasound and computed tomography before using the abbreviated form. Would suggest rephrasing this sentence to “Drainage of liver abscess may be achieved percutaneously (ultrasound or computed tomography guided) or surgically (via laparoscopic or open approach).

Reply 3: Thank you for the comment, we changed it as suggested

Changes in the text; we replaced “Drainage of liver abscess can be achieved either percutaneously US/CT guided or surgically; standard open or laparoscopic” with “Drainage of liver abscess may be achieved percutaneously (ultrasound or computed tomography-guided) or surgically (via laparoscopic or open approach).” Check line 83:85

- line 96 - “antibiotics” is more appropriate than “medications”

Reply 4: Thank you for the comment, we changed it as suggested

Changes in the text; we replaced medications with antibiotics check line 99

- line 101 - typing error, should be “PNA” instead of “PND”

Reply 5; Thank you for the comment, we changed it in the text by replacing PND with PNA check line 104

methods

- please do not bold the tables cited (unless this is required as per the journal formatting requirements)

Reply 6; Thank you for your comment we accepted the suggestion

changes in the text; we removed the table bolding

- definition of success rate and clinical improvement

Reply 7: Thank you very much for your suggestion. We edited Table 1 accordingly adding the definition of success rate for each RCT, we also gave a brief definition in the text

changes in the text, “clinical resolution of infection and radiological evidence of abscess resolution, either total disappearance or more than 50% decrease in the longest diameter before intervention for detailed definition check Table 1” line 126 : 128

results

- 3.1 - characteristics of included studies - please include the overall mean age used across studies, as well as overall % of males and co-morbidities. co-morbidities especially diabetes mellitus, underlying

biliary disease and malignancy are known factors to impact mortality in liver abscess. please also include this here.

Reply 8, thank you for the comment, we reported the mean age for each study, as well as the % of males and co-morbidities. co-morbidities especially diabetes mellitus and underlying biliary disease, whenever it is reported by the study in table 2, some studies did not report the exact mean and SD but reported a range instead, so it is nearly impossible to include the exact overall mean, many studies did not mention diabetes as a co morbidity, and we mentioned the available information according to each included study.

Changes in text: “1626 patients (79%) were males”

- line 221 - please explain what b refers to. in this case, does this mean decrease in success rate by 3.4% per cm increase of abscess size? b is not commonly used in scientific reports

Reply 9: Thank you for pointing this out. b refers the meta-regression coefficient and it is frequently used to report meta-regression findings as in the following example:

<https://pubmed.ncbi.nlm.nih.gov/30117036/>

- line 223 - same as above comment

Reply 10: Thank you for pointing this out. b refers the meta-regression coefficient and it is frequently used to report meta-regression findings as in the following example:

<https://pubmed.ncbi.nlm.nih.gov/30117036/>

tables

- very difficult to read in view of formatting, please adjust the font size accordingly to make this more readable, e.g. table 2.

Reply 11; thank you for the comment we did as suggested.

Review Comments (Round 2)

Thank you for the revision in the manuscript. This manuscript is almost suitable for publication. However, there are still minor changes which will help improve the manuscript.

1. Table 2A: For the columns on the right, there appears to be a formatting issue for “no. of abscess solitary: multiple” and localisation of the PLA (right lobe and left lobe). The indentation for the column is very messy and is not aligned to the top header (refer to attached image)

Reply 1: Thank you for the suggestion we reformed the table to make it more readable.

2. Also, thank you for including the details on failure requiring surgical intervention and mortality (lines 222-257). However, the data presented may be difficult to read when done all in text. Please summarise this in a table (would suggest supplementary material). In the text, I would advise writing “the overall number of failures in PCD is xx / yy (%) and xx / yy (%) under 3.4.1 for success rate. and the same for mortality as well (under the relevant section. Then briefly write that the outcomes for each study is summarised in Table xx.

Reply 2: Thank you for the comment we accepted the suggestion, please check the results section, 3.4.1. Success Rate, 3.4.3. Procedure-related Adverse Events, and the supplementary material S2 table S4.

3. Discussion has been much improved. Thank you.

For the line “Radiology plays a key role in determining the prognosis of pyogenic liver abscess (46, 47), gas formation was shown to be associated with higher mortality (48, 49), multiple loculi within the abscess, and increased size of the abscess were all predictors for percutaneous drainage failure (50, 51)”

I would suggest rephrasing as:

“Radiology plays a key role in determining the prognosis of pyogenic liver abscess (46, 47), multiple loculi within the abscess, and increased size of the abscess were all predictors for percutaneous drainage failure (50, 51).” And to add in “Literature on the impact of gas formation on clinical outcomes however is equivocal (48,49).”

Under gas formation, please also cite “Chan KS, Thng CB, Chan YH, Shelat VG. Outcomes of Gas-Forming Pyogenic Liver Abscess Are Comparable to Non-Gas-Forming Pyogenic Liver Abscess in the Era of Multi-Modal Care: A Propensity Score Matched Study. *Surg Infect (Larchmt)*. 2020 Dec;21(10):884-890. doi: 10.1089/sur.2019.278. Epub 2020 Mar 27. PMID: 32216699.”

Reply 3: Thank you for your patience and comments that helped in improving our manuscript, we did it as suggested. Page 15, line 304: 307 in the clean copy of the manuscript.