

RESPONSE TO THE REVIEWERS (Manuscript ID: 76077)

Dear Editors and Reviewers,

Thank you for your valuable comments and suggestions about our manuscript entitled "Amebic liver abscess: clinico-radiological findings and interventional management" (manuscript no 76077:, minireviews). These are very helpful for revising and improving our manuscript.

In the revised manuscript we have incorporated all the changes as suggested by the reviewers. Revised portion are underlined in the paper. Moreover, the revised manuscript has been edited for proper English language by a profession body (certificate included). Our point-by-point responses to the issues raised in the peer review report are as follows:

1.Response to reviewers' comments

Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: I enjoyed reading the manuscript. I understand the focus is narrow - uncomplicated abscess is not discussed.

Authors' response: We are extremely thankful to the reviewer for his positive comments. We hope readers of the manuscript will also enjoy the manuscript.

1. You have described 3 types of ALA - including subacute mild and thus i feel omit the "complicated" from the title. I feel this review should apply to every ALA - regardless of uncomplicated or complicated. Agree that you did focus on complicated things more.

Authors' response: As per reviewer's suggestion, the complicated word has been omitted from the title.

2. I find some fault with 3 citations for one study - pls check this. In a study of 317 patients with ALA, Balasegaram reported acute fulminating infection in 13% of cases [13, 20,51].

Authors' response: We thank the reviewer for pointing out this error. We have placed the correct reference.

3. Citation 18 is improper format - check it. The patients often present more acutely (< 10 days) with signs of severe disease including systemic toxicity, high fevers and chills, and an exquisitely tender hepatomegaly 18.

Authors' response: We have corrected the format in the revised paper.

4. Full stop is missing from the sentence - Signs related to rupture and other complications may be present

Authors' response: Full top has been placed.

5. Nice images. I feel sometimes the type II and type III can be confusing on the CT scan if the contrast enhancement is faint or if the IV contrast is suboptimal and sometimes if patient is already on therapy than though by timepoint patient may qualify as subacute; he may have features of chronic ALA. Some discussion on this is necessary. Is this classification validated? Need some comments and discussion.

Authors' response: We agree with the reviewer's opinion that it may not always be possible to differentiate one type from another type particularly when the intravenous contrast is suboptimal. Also, although most abscess fall in a specific category, there may be some abscesses with indistinct or overlapping CT features, not precisely fitting into a particular

category. Similarly, there may be overlapping between the three clinical patterns (acute, subacute and chronic) along the timeline. However, at a point of time, the clinical subtypes generally match with the imaging subtypes. We added a line in the revised manuscript addressing this issue. We now state that imaging features are distinct but overlap between the categories (page 13, Line 16-18). Although this classification is recently published and has not been validated, it is somewhat similar to the previously published sonographic classifications (reference 46, 65, 66). In the revised manuscript we have discussed the previous studies that led support to this classification (Reference no 38, 39,43, 46, 47, 65,67, 66).

6. Full form of ERCP is needed. Check this - In such cases, the diagnosis may be confirmed when ERCP or cavitogram demonstrates contrast extravasation into the abscess cavity [54].

Authors' response: The revised manuscript contains the full form of ERCP.

7. Also need to add that stenting or sphincterotomy are essential to control bile leak prior to abscess drain removal.

Authors' response: We agree with the reviewer that endoscopic sphincterotomy or stenting is essential to control bile leak prior to abscess drain removal in some cases where the fistulous communication persists despite prolonged percutaneous drainage. This line has been added in the revised manuscript (page 23, line 6-8)

8. The following statement is correct and i hope you could add some discussion that the contrary is true for pyogenic abscess. Check this -""The pus cultures rarely yield positive results. This is because most patients are generally pretreated with antibiotics."" In general, blood culture is negative for pyogenic liver abscess but pus culture is positive. This is contrary to what you mention for ALA (i do agree with you). Needs 1-2 sentences to compare and contrast.

Authors' response: We have clarified this statement in the revised manuscript.

9. I dont see any mention on laparotomy or laparoscopy and any data being included in the discussion section. Pls check and if literature mentions, include 2-3 sentences in this.

Authors' response: A new paragraph addressing the current use of surgery has been added in the last.

10. I also dont see mention about CRP or Procalcitonin role in diagnosis. I see white cell count stated. May be add 1-2 sentences on CRP or procalcitonin (if any data have)

Authors' response: CRP or Procalcitonin are important nowadays. We thank the reviewer for the suggestion. We have added relevance to these markers. In our experience and the available data suggest that both CRP and procalcitonin are raised in most cases, CRP more frequently than procalcitonin. We have added a line in the section of laboratory evaluation.

Reviewer #2:

Scientific Quality: Grade D (Fair)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Main Comments:

(1) This manuscript deals with amebic liver abscess, its diagnosis, classification and treatment. The authors provide an overview on the subject, focusing on severe and complicated subtypes; illustrative pictures are included.

Authors' response: We thank the reviewer for the comments.

(2) Many repetitions within the text make it lengthy for the reader, please be more concise.

Authors' response: We have thoroughly revised the manuscript and several sentences that were irrelevant expressing the same idea have been removed.

(3) As for the clinico-radiological correlation, more robust data/citations would be expected.

Authors' response: Most data about the clinic-radiological correlation has been derived from our recent work (Reference no 10). However, there are several other studies that support the idea of classifying imaging features of ALA into three types (reference 46, 65, 66). In the revised manuscript, we have cited and discussed those studies to back up this claim (Reference no 38, 39,43, 46, 47, 65,67, 66). We have also provided a historic context concerning the imaging classification.

Specific Comments/Suggestions:

(4) Risk factors, page 6: "Additionally, the disease in men is more complicated than women" -> Additionally, the disease is more complicated in men than in women.

Authors' response: We thank the reviewer for pointing out this error. This sentence has been corrected.

(5)Pathogenesis (second paragraph), page 8: "liquefied necrotic tissue (chocolate-colored sterile pus)" -> liquefied necrotic tissue (chocolate-colored sterile "pus").

Authors' response: We thank the reviewer for pointing out this error. This sentence has been corrected.

(6) Clinical presentation, page 9: "The typical findings on physical examination is hepatomegaly with point tenderness in the intercostal spaces" -> The typical finding on physical examination is hepatomegaly with point tenderness in the intercostal spaces; "and an exquisitely tender hepatomegaly 18" -> and an exquisitely tender hepatomegaly [18]; "...present In fact..." -> ...present. In fact...

Authors' response: We thank the reviewer for pointing out this error. These sentences have been corrected.

(7) Clinical presentation, page 11: "Leukocytosis in chronic abscesses suggest the presence of secondary infection" -> Leukocytosis in chronic abscesses suggests the presence of secondary infection.

Authors' response: We thank the reviewer for pointing out this error. The sentences have been corrected.

(8) Imaging evaluation, page 13: "The overall diagnostic accuracy of CT is more than ultrasound" -> The overall diagnostic accuracy of CT is higher than of ultrasound.

Authors' response: We thank the reviewer for pointing out this error. The sentences have been corrected.

(9) Imaging classification and clinoradiological correlation, page 14: "the viable parenchyma that are yet to be necrotic" -> the viable parenchyma that is yet to be necrotic.

Authors' response: We thank the reviewer for pointing out this error. This sentence has been corrected.

(10) Rupture, page 15: "However, intrathoracic ruptures, particularly the intrapulmonary, is noted more frequently in chronic cases (type II or III abscesses)" -> However, intrathoracic ruptures, particularly the intrapulmonary ones, are noted more frequently in chronic cases (type II or III abscesses).

Authors' response: We thank the reviewer for pointing out this error. The sentences have been corrected.

(11) Intrathoracic rupture: Pleural empyema, Lung abscess, Hepatobronchial fistula, page 16: "invading through the both diaphragm and pleura" -> invading through both diaphragm and pleura.

Authors' response: We thank the reviewer for pointing out this error. The sentences have been corrected.

(12) Biliary complication: communication versus compression, page 18: "total bilirubin levels >2 mg/dL was present only in the patients with biliary complications" -> total bilirubin levels >2 mg/dL were present only in the patients with biliary complications.

Authors' response: We thank the reviewer for pointing out this error. The sentences have been corrected.

(13) Concurrent Colitis and Perforations, page 19: "diarrhea is found only in only 15 to 30% of patients with ALA" -> diarrhea is found in only 15 to 30% of patients with ALA.

Authors' response: We thank the reviewer for pointing out this error. The sentences have been corrected.

(14) Management: Role of image-guided percutaneous drainage (third paragraph), page 21: "In addition to clinical criteria, imaging based criteria for the use of drainage was formulated by De la Rey Nel et al., which is still widely used [8-10, 52]. They recommended that the abscesses greater than 10 cm should be drained as it takes a long time to resolve and are at risk of all types of complications. Furthermore, they suggested that the abscesses located in the left should be drained as it carries risk of rupture into the pericardium, a fatal complication with a high mortality" -> In addition to clinical criteria, imaging based criteria for the use of drainage, which are still widely used, were formulated by De la Rey Nel et al. [8-10, 52]. They recommended that the abscesses greater than 10 cm should be drained as they take a long time to resolve and are at risk of all types of complications. Furthermore, they suggested that the abscesses located in the left lobe should be drained as they carry a risk of rupture into the pericardium, a fatal complication with a high mortality.

Authors' response: We apologize for these errors and thank the reviewer for suggestions. All sentences have been revised accordingly.

(15) Needle aspiration versus catheter drainage, page 23: "abscesses that liquefies over a period of time" -> abscesses that liquefy over a period of time.

Authors' response: We apologize for this error. This sentence has been corrected.

(16) Percutaneous drainage in management of complications (third paragraph), page 23: "it also effectively treats pleuropulmonary ruptures 14" -> it also effectively treats pleuropulmonary ruptures [14].

Authors' response: We apologize for this error. This sentence has been corrected.

(17) Figure legend 4: "for more than 4-weeks" -> for more than 4 weeks.

Authors' response: We apologize for this error. This sentence has been corrected in the revised manuscript.

(18) Figure legend 5: "The fluid collection that is localized in the subphrenic space (asterisk)" -> A fluid collection is localized in the subphrenic space (asterisk).

Authors' response: We apologize for this error. This sentence has been corrected in the revised manuscript.

Reviewer #3:

Main comments :

1. I really like the idea of correlating imaging findings, lab findings, and clinical status to types of ALA. This could be helpful for prognostication and the decision for intervention. This could be a helpful way to stratify these variable patients. However, I do not feel that

the paper provides convincing evidence for radiologic stratification as stated currently. There are few references or statistics connecting clinical courses to imaging findings in the paper.

Authors' response: We would like to thank the reviewer for carrying out a thorough critical analysis of the manuscript, for providing the constructive comments, and for appreciating the core idea of the manuscript (clinico-radiological correlation).

The major clinical and imaging data supporting this classification come from our recently published paper (reference no 10, 68). However, the idea of classifying the variable imaging appearance into three types is not new. In 1987, Leonetti et al., in 1997, N'Gbesso et al., and in 2008, Nari et al., have published a similar classification in non-English literature, although it was based on sonographic examination. In addition, there are many studies that indicate morphological variations as ALAs evolve through different stages, from acute to chronic. Gross morphology from autopsy series further provide convincing evidence to support this concept. In the revised manuscript, we have discussed and added several new references including historical data that support the radiologic stratification (Reference no 38, 39,43, 46, 47, 65,67, 66).

2. Additionally, given the review's emphasis on clinoradiological findings, there is too much emphasis on pathogenesis. It could be helpful to create a figure breaking down the radiologic, clinical, and management considerations unique to the three types of ALA. If the paper was streamlined with concise breakdowns of clinical presentations and radiologic findings for each patient type followed by management considerations for each patient type, it would be a very helpful manuscript.

Authors' response: According to the reviewer's suggestion, we have removed the first paragraph from the pathogenesis section. Also, we have created a table (Table 1) breaking down the radiologic, clinical, and management considerations unique to the three types of ALA as suggested by the reviewer. This would help the readers understand the key concept of the manuscript with clarity.

3. Additionally, there are many grammatical and syntax errors that if corrected would greatly improve the manuscript. I have included some other recommendations and thoughts on the page below.

Authors' response: We have revised the entire manuscript for the grammatical and syntax errors. Also, the revised manuscript has been edited by a professional language editor for the quality and accuracy. We hope the edited manuscript does not suffer from grammatical and syntax errors.

General comments

1. Would try and include primary sources of information, especially when a review is used for a single point made in the manuscript

Authors' response: In the revised manuscript, we have tried to include the original source of information whenever possible. Accordingly, references have been thoroughly updated.

2. Page 2 Line 9 - delete "the" before antibiotics

Authors' response: The article "the" has been removed before the antibiotic.

3. Line 10 - do not need "frequently" twice

Authors' response: The line 10 has been revised accordingly.

4. Line 20-22 - each line repeats the same concept, could be more concise

Authors' response: The line 20-22 has been revised to make the concept more concise.

5. Page 3 Line 13 - It mentions there are only two forms here, but a third form is mentioned earlier: mild form

Authors' response: The sentences have been rephrased in the revised manuscript.

6. Page 4 Line 3 - please clarify that EH is not a natural colonizer, but only colonizes those who have been exposed and even they are not all colonized for life

Authors' response: The first paragraph of the introduction section has been thoroughly updated, omitting this line.

7. Line 5 - Can be restated just that ALA is the most common and has the highest mortality of amebiasis manifestations

Authors' response: This sentence has been revised according to the suggestion.

8. Line 7 - "Estimates" instead of "estimated"

Authors' response: The line 7 has been revised in present tense as suggested by the reviewer.

9. Line 5 - references are quite old and may have some less than modern epidemiological estimations

Authors' response: Unfortunately, we could not find any reliable recent data on the global morbidity and mortality from amoebiasis than what was reported by Walsh JA in 1986 (Reference 1). In the revised manuscript, we have added recent data that mentions PCR based prevalence estimates of EH in the stool samples (reference 27).

10. Line 12 - please include citation for mortality reduction

Authors' response: The revised manuscript includes the citation for the mortality reduction (reference number no7).

11. Line 13 - Given the statement that most patients are asymptomatic at baseline, please give context for “becoming asymptomatic”

Authors’ response: This statement “ Most patients become asymptomatic within 72 to 96 hours of treatment” is in the context of ALA with mild symptoms, not in the context of asymptomatic ALA.

12. Line 14 - can delete “It is considered that”

Authors’ response: This phrase has been deleted

13. Page 6 Line 5 - “Even in endemic countries, ALA occurs primarily in rural areas where defecation in open air is a common practice” would include citation for this

Authors’ response: A new reference has been added to support this point. In fact, there were references in the submitted manuscript placed in the next line. Now we have put those references after line 5.

14. Line 13-15 Multiple lines that repeat the same idea, could be more concise.

Authors’ response: We have deleted a line in the revised manuscript to make it more concise.

15. Page 7 Line 10 - 1% is quoted as frequency of ALA, but 1-10% is used earlier in the manuscript

Authors’ response: We thank the reviewer for pointing out this error. This error has now been corrected.

16. Page 8 Line 11 - Would clarify this is a mature wall that indicated chronicity/2’ infection as opposed to the wall mentioned as ragged in line 3

Authors' response: A line has been added saying that a persistent abscess with a mature wall indicates chronic abscess with or without secondary infection.

17. Line 15 - Wording is somewhat misleading as it says above they are usually solitary, but that 60% of autopsy samples have multiple. Is this because autopsy samples are from patients with more severe courses? Or is it because imaging findings are incongruent with post-mortem findings?

Authors' response: These lines meant that solitary abscesses predominate in clinically diagnosed and successfully treated series, whereas large and multiple abscesses are usually reported in autopsy series. In other words, this implies that large and multiple abscesses are more often associated with fatal cases. We have changed the wording in the revised manuscript.

18. Line 17 - Please define "western" populations vs asian populations

Authors' response: By Asian population, it meant South-eastern countries such as India, Sri Lanka, Pakistan and Bangladesh and by western population, Mexico, Central America. Considering the available data, we have revised this line comparing southeast Asian population with other studied populations.

19. Page 9 Line 7 - Finding instead of findings, but this line can also be removed as it mentioned immediately above

Authors' response: We have corrected the error. Also, the repeated clinical feature (hepatomegaly) has been removed.

20. Line 9 - Most patients will have elevated Alkaline Phosphatase and some but not all patients will have transaminitis. There is even some suggestion they can be used to predict size of abscess/severity of disease (<http://dx.doi.org/10.18203/2320-6012.ijrms20173158>)

Authors' response: We agree with the reviewers that most patients have elevated alkaline phosphatase but elevated transaminases are found in a small proportion of cases. Also, elevated transaminases might be indicative of severe disease. We have added a line pointing out this information.

21. Line 17 - "The prevalence of this type of ALA may be high in endemic areas (up to 60%)." → would include citation

Authors' response: A citation has been included for this line.

22. Line 20 - Number 18 is present without context

Authors' response: There was error in formatting the reference no 18; this has been corrected in the revised manuscript

23. Page 11 Line 16 - Would address the lack of specificity and frequency of seropositivity in endemic countries considering this is the population of interest for the severe subtypes and how this can make diagnosis difficult

Authors' response: We have added a few lines addressing the usefulness of serological tests, its sensitivity and specificity, and its limitations, particularly in the endemic areas.

24. Page 12 Line 12 - "Most common employed modalities" → for diagnosis of ALA.

Authors' response: The suggested phrase has been added with this line.

25. Line 15 - Would add citation for why MRI seems to offer no advantage

Authors' response: A citation has been added explaining why there are no additional advantages of MRI in ALA.

26. Page 13 Line 2 - Would include numbers in terms of sensitivity/specificity between CT/US for diagnosis to improve this claim

Authors' response: Sensitivity of ultrasound varies from 85 to 95% and CT has higher sensitivity (100%) than ultrasound. These lines have been added in the revised manuscript (page 10, line 20-21). Both tests were well-known for the nonspecific findings and we could not find any noteworthy study mentioning the specificity of these modalities.

27. Page 18 "The diagnosis of superinfection can be made when the needle aspirate changes its odor and color from odorless and chocolate-brown color to foul smelling and purulent [14, 43]." - I do not think this is supported by the works cited, and does not seem reliable method of this determination

Authors' response: This line has been deleted from the revised manuscript

28. "On imaging, the secondarily infected abscesses demonstrate rim enhancing wall (type II pattern) similar to pyogenic abscesses." - needs citation

Authors' response: We have deleted this line from the manuscript considering lack of convincing evidence.

29. Page 20 Most experts recommend therapy with an intraluminal agent after metronidazole for elimination of potential intraluminal cysts

Authors' response: We have included a line mentioning the use of intraluminal agent after metronidazole for elimination of potential intraluminal cysts.

30. Section: Imaging classification and clinicoradiological correlation - I feel that this section is the crux of the paper and has little to no clinical data to support the type of imaging seen and its connection to the patient outcome. How is the connection between the imaging and clinical course made? Is it based on case series, personal experience? Please elaborate.

Authors' response: The major clinical data to support imaging classification and clinico-radiological correlation come from our recently published series (Reference no 10, 68). In addition, there are several sonographic studies that lend support to the imaging classification. In the revised manuscript, we cited several studies to back up the claim of clinicoradiological correlation and the imaging classification (Reference no 38, 39,43, 46, 47, 65,67, 66).

6 EDITORIAL OFFICE'S COMMENTS

(1) Science editor:

This review briefly outline the clinical and imaging features of the three distinctive forms of the ALA and discuss the role of percutaneous drainage in management of ALA. The three reviewers put forward more comprehensive opinions on the full text, and the authors need to read them carefully and answer or make revisions one by one.

Language Quality: Grade A (Priority publishing)

Scientific Quality: Grade C (Good)

Authors' response: Thank you for your valuable comments. The manuscript has been thoroughly revised in the light of peer-review Report, editorial office's comments and the criteria for manuscript revision. New portions are underlined in the paper. The revised manuscript has been edited by a competent agency (of native English-speaking editors) for English language and a high quality has now been reached.

(2) Company editor-in-chief:

I recommend the manuscript to be published in the World Journal of Clinical Cases. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures

(in which all components are movable and editable), organize them into a single PowerPoint file.

Authors' response: Thank you sir for the acceptance of our work. The manuscript has been thoroughly revised in the light of peer-review Report, editorial office's comments and the criteria for manuscript revision. We are providing the images on PowerPoint slide which can be reprocessed by the editors. All the figures and tables are original.

Best regards,

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