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OPEN PEER REVIEW

Long-term Follow-up of Hepatobiliary Fascioliasis: Serologic and Computed Tomography Findings

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

6 comments · 31 Mar 2024 – 29 Jun 2024

Reza Jafari-Shakib Reviewer

MAJOR REVISION 31 Mar 2024

I reviewed the manuscript entitled " Long-Term Follow-Up of Hepatobiliary Fascioliasis: Serologic and Computed Tomography Findings". In this study, anti-Fasciola antibody titer and radiological improvement were assessed during a long-term follow-up after treatment of hepatobiliary fascioliasis. It is an interesting topic, but the following concerns need to be addressed in the manuscript.

Abstract

– It seems that parasitic is not suitable as a keyword.

– Asymptomatic patients or treated patients?

Introduction

– The 4 periods must be explained. "The second and fourth periods, in which almost all patients are diagnosed, are the most important"

– How about MRI? "For the diagnosis of HF, computed tomography (CT) is an exclusive imaging method for the hepatic period."

Methods

– Is it possible for FH eggs to appear in the stool during the hepatic period? From CDC: "The chronic phase is also referred to as the biliary or adult phase. The chronic phase begins when immature larvae reach the bile ducts, mature into adult flukes, and start producing eggs. The eggs are passed from the bile ducts into the intestines and then into the feces."

– Which method was used by the investigators to detect FH eggs? Explain it in detail.

– Was ERCP done for all patients?

– Was Pearson/Spearman correlation analysis performed to assess the relationship between variables in this study?

Result

– It is better to write the reference range for all tests in the tables.

– Eosinophil (n/mm3): 2.027 ± 2.197 or 2027±2197? The same question applies to WBC.

– Total bilirubin (mg/dL) was exactly the same before and after treatment.

– - or 0 in table 2?

– The first Fig has been indexed as (b) and the recovery fig as (a).

– I am not sure the section in Fig 1a is at the same level as that in Fig 1b.

It is better to revise some sentences as follows:

– When the parasite advances to its main localization, the biliary tract and fragments of hepatocytes lead to the peripheral cavity and abscess which can last several months. This period is the hepatic period.

– the absorbance value was calculated according to the following formula: ELISA titer DU/mL 11 >Positive.

– Du or DU/ml? ELISA titer DU/mL 11 >Positive

– Pretreatment and follow-up CT? "The time between diagnoses and compared CT imaging times varied between 12 and 56 months (mean: 39.2 ± 12.9 months). Pretreatment and follow-up CT?"

– "due to the lack of patients" or not enough patients.

– Delete "It is known that ultrasonography has low sensitivity in the hepatic period due to the heterogeneous structure of the liver." due to repetition.

– Delete "A p-value less than .05 was accepted as statistically significant" in Table 2.

Some typo corrections are listed below:
– Hepatobiliary Fascioliasis
– 1), 11), 111)
– negativity7, hepatic period2 as references
– Hepatomegali
– Italicize “Fasciola hepatica and Fasciola gigantica”.

The manuscripts must be checked by a native English speaker.

Arash Letafati Reviewer

MAJOR REVISION 26 Jun 2024

In the abstract, clarify this phrase: "Previous studies showed long-term radiological findings." It should be more specific.
In the Materials and Methods section of the abstract, please include the year of the study and the collaborating laboratory/hospital.
During the experiment, did you observe a drop in eosinophil levels over time?
I did not understand your conclusion: "Radiological imaging and antibody levels should be carefully interpreted in asymptomatic patients." What do you mean by "carefully interpreted"? Add a sentence after this to explain the reason, based on the results, such as in relation to eosinophil counts.
Does the ELISA kit provide borderline results? If so, how were these borderline cases handled? Were they considered positive or negative?
Were all patients evaluated for their immune status (e.g., transplant recipients, immunodeficient)? This affects antibody levels. This should be stated clearly, and if immune status was not evaluated, this should be mentioned as a limitation in the discussion section.
The article has numerous grammatical errors that need to be corrected. Consider using Grammarly Premium or a native English speaker for assistance.

Ensiyeh Rahimi Reviewer

ACCEPT 27 Jun 2024

1. The title and abstract cover the main aspects of the work.
2. The flow of the paper is reasonable and has a logical flow.
3. There are no significant language issues.
4. There are not many studies available in this field, and this paper is helpful. On the topic of fascioliasis, most of the studies are case reports. In this manuscript, the number of cases studied is desirable.
5. Also, the advantage of this study is that the patients have been followed for a long time.
This paper is acceptable for publication.
It is recommended to use ultrasound along with CT scans in future studies for greater clarity of imaging changes.

Referee 1 Reviewer

MAJOR REVISION 29 Jun 2024

Dear AE,
This study evaluated 25 patients with hepatobiliary fascioliasis, finding significant decreases in eosinophil counts and Fasciola antibody levels, with 40% achieving antibody negativity and notable radiologic improvements. The results suggest that antibody negativity and radiologic improvements take time,

requiring careful interpretation during follow-up.
The study design and data analysis appear robust, but there are a few potential areas that might be considered as limitations or failures:
-Some sentences lack references. All sentences quoted from other articles must have references at the end. For example, the following sentences:
“The parasite reaches the liver through the peritoneal cavity by passing through the intestinal wall after oral ingestion. When the parasite advances to its main localization, the biliary tract and fragments of hepatocytes lead to the peripheral cavity and abscess which can last several months.”

Introduction
-The background is generally well-covered, but it could benefit from more details on the long-term implications of fascioliasis and the importance of this study in the current context.
Suggestion: Expand on the significance of long-term follow-up and how this study fills existing knowledge gaps.
Methods
- Clearly present key elements of the study design early in the methods section.
Setting.
-Please provide a more detailed justification for the chosen sample size, possibly with a power calculation.
Results
-The manuscript does not clearly provide reasons for non-participation at each stage.
Suggestion: Include reasons for non-participation and consider using a flow diagram to illustrate the participant flow.
-As “recommendations for further study,” what would you offer to other researchers in the field? Include these at the conclusion of the paper.
-Please review more recent and updated articles for your study instead of old references to improve the quality of the rationale for your study.

Associate Editor

MAJOR REVISION 29 Jun 2024

Dear EIC,
This retrospective cohort study evaluated long-term laboratory findings, antibody levels, and radiological features in 25 patients with hepatobiliary fascioliasis (HF) after treatment, showing significant decreases in eosinophil counts and Fasciola antibody levels, with 40% of patients achieving antibody negativity and notable radiologic improvements in liver lesions, lymphadenopathy, and splenomegaly. The study concludes that both antibody negativity and radiological improvement can take a long period to develop, suggesting careful interpretation of these parameters during follow-up in asymptomatic patients.
The manuscript is a valuable piece of research. But some revisions are needed. The authors should revise it based on the REVIEWERS' comments. Also, minor changes should be made to the abstract:
1- The study design should be mentioned in the first line of the method section of the ABSTRACT.
2- A summary of the statistical analysis results should be mentioned in the result section of the ABSTRACT.

Editor-in-Chief

MAJOR REVISION 29 Jun 2024

Dear Author,
Thank you for submitting the article. It needs some revision. Please revise it based on the reviewers' and AE's comments.

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Reviewer 1,

First of all, I would like to express our gratitude for your contributions to our article. I hope you will excuse my delay in replying due to some personal problems. Your criticisms and suggestions have been answered and corrected as follows. I made the changes you requested in the article (highlighted in yellow color).

Best regards.

Abstract

1− It seems that parasitic is not suitable as a keyword.

- The word parasitic was removed from the keywords.

2− Asymptomatic patients or treated patients?

- The words asymptomatic patients were replaced with treated patients.

Introduction

3− It must be explained the 4 period. "The second and fourth periods, in which almost all patients are diagnosed, are the most important"

- Added new information about the four periods.

4− How about MRI? "For the diagnosis of HF, computed tomography (CT) is an exclusive imaging method for the hepatic period."

- The sentence was edited as "For the diagnosis of HF, magnetic resonance imaging and computed tomography (CT) are an exclusive imaging methods for the hepatic period" and a new refference was added.

Methods

5− Is it possible appearance of FH eggs in the stool are happened in hepatic period? From CDC: "The chronic phase is also referred to as the biliary or adult phase. The chronic phase begins when immature larvae reach the bile ducts, mature into adult flukes, and start producing eggs. The eggs are passed from the bile ducts into the intestines and then into the feces."

- In the hepatic period, no eggs are seen in the feces. During this period, the ELISA test becomes positive. The migration of larvae from the liver parenchymal tissue continues towards the bile ducts, they reach the bile ducts after 3 months, become adults and start laying eggs. During the biliary period, eggs begin to

appear and the diagnosis was confirmed by seeing the parasite itself in ERCP or eggs in the feces. The necessary revision was made in the method section.

6− Which method was used for FH eggs detection by investigators? Explain it in detail.

- Egg detection method was added in detail to the method section. New reference was added for this.

7− Was ERCP done for all patients?

- We performed ERCP in only 3 (12%) patients because they had clinical or laboratory findings compatible with extrahepatic biliary obstruction. The diagnosis of fascioliasis in these patients was confirmed by extraction of live, mobile *Fasciola hepatica* from extra-hepatic biliary ducts during ERCP. This sentence was added to the results section.

8− Was Pearson/Spearman correlation analysis performed for the relationship between variables in this study?

- A correlation was made between pre-treatment and follow-up variables. The findings were stated in the results section.

Result

9− It is better to write the reference range for all tests in Tables.

- Normal reference range values were added to the table as a footnote.

10− Eosinophil (n/mm3): 2.027 ± 2.197 or 2027±2197? Also, for WBC.

- Eosinophil and WBC number spelling typos were corrected.

11− Total bilirubin (mg/dL) was exactly the same for before and after treatment.

- The exact values of pre-treatment and follow-up were 0.600±0.369 and 0.667±0.331, respectively. That's why it was written that way. It was written as 0.60±0.36 and 0.66±0.33 in the table.

12− - or 0? In table 2?

- It was written as 0 in the table.

13− The first Fig has been indexed as (b) and the recovery fig as (a).

- The image (a) showing the lesions with arrows is the pre-treatment image (date 27.04.2011) and figure 1b shows the post-treatment image (date 12.09.2014). There is no error in indexing.

14− I am not sure the section in Fig 1a is the same level in Fig 1b.

- Since the patient was mobile during the second CT scan, the radiologist (İ.A. selected the closest and most accurate image to the localization of the first image.

It is better to revise some sentences as below:
15− When the parasite advances to its main localization, the biliary tract and fragments of hepatocytes lead to the peripheral cavity and abscess which can last several months. This period is the hepatic period.

- The sentence has been changed.

16− the absorbance value was calculated according to the following formula: ELISA titer DU/mL 11 >Positive.

- The sentence has been corrected.

17− Du or DU/ml? ELISA titer DU/mL 11 >Positive

- The sentence has been corrected.

18− Pretreatment and follow-up CT? "The time between diagnoses and compared CT imaging times varied between 12 and 56 months (mean: 39.2 ± 12.9 months). Pretreatment and follow-up CT?"

- The sentence has been corrected.

19− "due to the lack of patients" or not enough patients.

- The sentence has been corrected.

20− Deletion of "It is known that ultrasonography has low sensitivity in the hepatic period due to the heterogeneous structure of the liver." due to repetition.

- The sentence has been removed.

21− Deletion of "A p-value less than .05 was accepted as statistically significant" in Table 2.

- The sentence has been removed.
-

22. Some typo corrections are listed below:
− *Hepatobiliary Fascioliasis*
− *ı), ıı), ııı)*
− *negativity7, hepatic period2 as reference*
− *Hepatomegali*
− *And in Italic in “Fasciola hepatica and Fasciola gigantica”*

- All typos have been corrected.

23. The manuscripts must be checked by an English language native speaker.

- The manuscript is planned to be checked by the journal's editorial service.

Dear Reviewer 2,

First of all, I would like to express our gratitude for your contributions to our article. I hope you will excuse my delay in replying due to some personal problems. Your criticisms and suggestions have been answered and corrected as follows. I made the changes you requested in the article (highlighted in green color).

Best regards.

1- In the abstract, clarify this phrase: "Previous studies showed long-term radiological findings." It should be more specific.

- The sentence was corrected and changed by using clearer wording.

2- In the Materials and Methods section of the abstract, please include the year of the study and the collaborating laboratory/hospital.

- The hospital information and dates of the study were added to the materials and methods section.

3- During the experiment, did you observe a drop in eosinophil levels over time?

- During the follow-up period, we observed a decrease in eosinophil levels over time. The mean eosinophil count (n/mm3) was 2,027 (n=25) pre-treatment, 827 (n=10) in the fourth week, 458 (n=19) in the twelfth week, and 219 (n=12) in the twenty-fourth week. These data were added to the results section.

4- I did not understand your conclusion: "Radiological imaging and antibody levels should be carefully interpreted in asymptomatic patients." What do you mean by "carefully interpreted"? Add a sentence after this to explain the reason, based on the results, such as in relation to eosinophil counts.

- The sentence was corrected and changed by using clearer wording.

5- Does the ELISA kit provide borderline results? If so, how were these borderline cases handled? Were they considered positive or negative?

- The cut-off value of the kit was 10; patient sera with a >11.0 DRG units = DU/mL [DU = patient absorbance value × 10 / cut-off (C1 + C2 / 2)] were determined to be seropositive. For patients with results within the cut off value; a) ELISA method was repeated after 15 days. b) The possibility of cross reactions (hydatid cyst, schistosomiasis and toxocariasis) was taken into consideration. (This information was added to the materials and methods section)
- We had one patient in this situation. The anti-Fasciola Ab value at the time of diagnosis was 12 DU/ml and the value repeated twice at 15-day intervals after treatment (22nd mounth) was 11 DU/ml. No parasitic disease that could cause cross-reaction was detected. This patient was recorded as positive.

6- Were all patients evaluated for their immune status (e.g., transplant recipients, immunodeficient)? This affects antibody levels. This should be stated clearly, and if not evaluated, mentioned as a limitation in the discussion section.

- None of our patients had transplant recipient, chronic liver disease, chronic kidney disease, haematological disease, immunosuppressive drug use in the medical record review. This missing information was corrected by adding it to the method section.

7- The article has numerous grammatical errors that need to be corrected. Consider using Grammarly Premium or a native English speaker for assistance.

- The manuscript is planned to be checked by the journal's editorial service.

Dear Reviewer 3:

First of all, I would like to express our gratitude for your contributions to our article. I hope you will excuse my delay in replying due to some personal problems. Your criticisms and suggestions have been answered and corrected as follows. I have added your requested change to the discussion section of the article (highlighted in blue).

Best regards.

It is recommended to use ultrasound along with CT scan in future studies for more clarity of imaging changes.

-I have added your requested change to the discussion section of the article.

Dear Reviewer 4:

First of all, I would like to express our gratitude for your contributions to our article. I hope you will excuse my delay in replying due to some personal problems. Your criticisms and suggestions have been answered and corrected as follows. I have added your requested change to the related parts of the article (highlighted in blue).

Best regards.

1 -Some sentences lack references. All sentences quoted from other articles must have references at the end of themselves.

-Reference numbers have been added or new reference numbers have been given to sentences where no reference is reported.

2- Introduction
-The background is generally well-covered, but it could benefit from more details on the long-term implications of fascioliasis and the importance of this study in the current context.

-As you suggested, we have added the contributions to follow-up of our study results and the parts that have not been emphasised in the previous studies in the introduction section.

3- Methods
- Clearly present key elements of the study design early in the methods section.

-In this study, the effect size=0.5 (using Cohen's criteria), alpha=0.05 and power=0.85, and the minimum required sample size was determined as n=40. However, only 25 patients could be included in the study due to the reasons stated in the flow chart below. This issue was emphasised as a limiting factor of the study in the discussion section of the article.

4- Results
-The manuscript does not clearly provide reasons for non-participation at each stage.

-The reasons why patients could not be included in the study were shown in the results section with a flow diagram.

5-As "recommendations for further study," what would you offer to other researchers in the field? Include at the conclusion of the paper.

- Recommendation for further work have been added.

6-Please, investigate more recently articles for your study as well as updated ones instead of old references, in order to improve the quality of purpose behind your study.

-New articles on fasciolasis have been reviewed and some of them that are relevant to our article have been added as new references.

2 Revision 1

4 comments · 27 Jan 2025 – 2 Feb 2025

Referee 1 Reviewer

ACCEPT 27 Jan 2025

Dear AE,
I reviewed the manuscript again. The great effort in improving the manuscript is highly appreciated.
The authors have addressed all comments.
Thank you

Reza Jafari-Shakib Reviewer

ACCEPT 31 Jan 2025

I reviewed the manuscript entitled " Long-Term Follow-Up of Hepatobiliary Fascioliasis: Serologic and Computed Tomography Findings". Many concerns have been addressed, but some minor concerns remain, as follows:
1. There is no need to italicize "Hepatobiliary fascioliasis".
2. The following needs to be revised: "based on parasitologically, immunological,"
3. The following needs to be revised: "long-term radiology findings"
4. Patients are usually asymptomatic during this period: "The incubation period, in which the first symptoms are observed following the ingestion of metacercariae"
5. How about F. gigantica metacercariae? "Humans are infected after consumption of water or water-related vegetables that are contaminated with F. hepatica metacercariae"
6. It is better to merge these sentences: "The third period of fascioliasis begins with the slow migration of the parasite in the liver parenchyma and lasts several months (2, 4). This period is the hepatic period."
7. It is better to write "magnetic resonance imaging (MRI)".
8. "Only" in this sentence is not suitable because diagnosis may also occur accidentally through stool examination or imaging: "Asymptomatic individuals during the latent period, which can last for months or years, can only be detected during family screening after the patient's diagnosis"
9. It is better to clarify this sentence and the numbers of patients (n=10), (n=19), (n=12): " The eosinophil count decreased over time and the mean eosinophil count declined to 827/mm3 (n=10), 458/mm3 (n=19) and 219/mm3 (n=12) at the fourth, twelfth and twenty-fourth weeks, respectively."
10. This writing is not common: "43.0 ± 10.3 months (±SD)"
11. It isn't mentioned that FH stands for Fasciola hepatica.
12. Is there any reference for the following statement? "The possibility of cross reactions (hydatid cyst, schistosomiasis and toxocariasis) was taken into consideration."
13. Reference 5 must be adjusted according to this journal's style.

Associate Editor

ACCEPT 1 Feb 2025

Dear EIC.
Previous errors have been corrected, and there are no further recommendations.

Editor-in-Chief ACCEPT 2 Feb 2025

Accept