

Peer Review File

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Reviewer A

It could be better clarified what characteristics the authors are referring to. By reading the article, it feels like the authors limit the characteristics to clinical.

1. This is a descriptive study conducted in Japan that aimed to describe the clinical characteristics of HCC in HIV/HCV co-infected haemophiliac patients.

Haemophiliacs are an important HIV/HCV risk group in Japan, and potentially other countries. However, the sample is very small and owing to a lack of sufficient contextual information, it is not very obvious that the article fills a critical knowledge gap with strong evidence. The study methodology also requires clarification in many aspects.

- Thank you for your comment. I guess this is a general comment, and we revised the manuscript as below.

2. Title: HIV/HCV co-infection as being due to contaminated blood products was not validated in the study

- Thank you for your comment. All of the patients in this study were victims of unheated contaminated blood product in Japan. We specified it in Introduction (line 89-90) and Results (line 148-150).

3. Abstract

The recruitment/sampling strategy is not apparent, and neither is the level of care in the setting in which they were identified. Data collection technique is also not clear, was it medical records that were reviewed or new data collected retrospectively?

- Thank you for your comment. I updated the methods, including the data collection technique in the Abstract (line 41), and in Methods (line 112-115).

4. Introduction

The introduction is brief and missing critical information on the burden of HIV-HCV co-infection in Japan as well as information relating to the current body of literature and knowledge gaps. My suggestion would be to move up some text in the Discussion to the Introduction to provide a better understanding of the context and background of the topic to the readers.

- Thank you for your suggestion. We added the importance of iatrogenic problem in Japan with new reference in Introduction (line 89-90), and moved the first part of Discussion to Introduction (line 96-105, 107-108).

5. Line 87: There are reports that the use of contaminated blood products occurred in Japan between the 70s and 90s. Could the authors clarify this (not only the 80s) and its impact on

HCV and HIV transmission?

- Thank you for your comment. Honestly, the actual points of contaminated blood product usage in some patients were not clear, but the majority of the problems generally occurred in early 80s, and in principle, the patients in this study were the victims of its period. I added the explanation with new reference in Introduction (line 89-90), and Results (line 148-150).

6. Lines 97-98: The aim needs rephrasing as it suggests that this was done within an existing Japanese multicentre study yet in the methods it seems that this was an independent multicentre study. The ‘multicentre study’ might be better left out here in the aim and described in the methods to mitigate this kind of confusion.

- Thank you for your comment. We agree with you, and updated the Methods (line 112-115).

7. Methods

Study design

It is not clear when this study was conducted. The title mentions that HIV/HCV coinfection from contaminated blood products, but how the iatrogenicity of HIV/HCV transmission was validated is not mentioned in the methods.

- Thank you for your comment. The all of the patients in this study were the victims of iatrogenic usage of unheated blood products. We added some mentions in Introduction (line89-90) and Results (line 148-150).

8. Lines 103-104: “.... 26 cases of HCC in coinfecting hemophilic patients were 104 accumulated from 8 centers, diagnosed between December 1999 and December 2017.” This is a result not method, and should be moved down to the relevant section. Moreover, how many such centres were approached and if any declined need to be highlighted.

- Thank you for your comment. We moved it to the Results with adding the centres including not respond to the first query (line 144-148).

9. What is the justification for the study period and for the selection of participants through centres that treat HIV, rather than say from the cancer register or haematological units with a register of haemophiliacs?

- Thank you for your comment. Actually, majority of the HIV positive patients were followed by HIV physicians rather than isolated haematologists in Japan, so that most of the cases were covered in this study with asking HIV physicians. I added the mention in Results (line 144-148).

10. Lines 105-106: As highlighted in the abstract, data collection described in the methods is not clear and should ideally indicate whether this was a review of medical records or that new data collected retrospectively. In the discussion there is also a mention of a survey which is not in the methods.

- Thank you for your comment. We described the procedure of data collection in Methods (line 112-115).

11. Line 105: Which outcomes? There is only one outcome, survival in the results.
- Thank you for your comment. We updated it as “survival after treatments” only (line 114).
12. Line 107: How do institutional protocols for HCC diagnosis vary in terms of sensitivity in Japan? It would be nice if the authors could you clarify why there is no standard national protocol in Japan
- Thank you for your comment. We added some mentions regarding this matter in Discussion, as one of the limitations of this study (line 276-282).
13. Patients
Lines 111-112: Ethics. Was consent sought from the participants? There needs to be an explanation why it wasn't necessary
- Thank you for your comment. We added the reason of unnecessary of written informed consent in Methods (line 123-126).
14. Statistics
Lines 115-116: Description is insufficient as the analyses include descriptive statistics. It would also be prudent to mention the effect measures (periodicity of survival) for the survival analysis and justification for the time intervals selected.
- Thank you for your suggestion. We updated the method of statistics (line 129-140).
15. Results
There seems to be a mix of results with discussion and this needs to be rectified.
Table 1 and 2 could be restructured. For categorical variables, each value should be presented on separate rows as has been done for the HCC primary treatment variable. However, HCC primary treatment variable should be restructured such that there is a row/category for no primary treatment.
- Thank you for your suggestion. We updated the Tables 1 and 2, and updated the statistics (line 129-140).
16. What is HCC number? Please rephrase
- Thank you for your comment. We rephrased it as “HCC nodule” in Table 1.
17. There are too many horizontal lines in the tables and the use of symbols for the footnotes is not in line with journal requirements. The use of * is reserved for p-values
- We apologize to use too many and unreserved symbols, and we deleted most of them because we believe the readers can follow without them. We changed one remaining symbol from * to in Table 2.
18. Line 121: It is mentioned that all patients were male and had haemophilia, but haemophilia was an inclusion criterion for the study and not a finding/result.
- All of the patients were haemophilia, and naturally, the men. We added the mention in Discussion (line 282-285).

19. Line 130-131: It is sufficient to mention that they had no HCV treatment history, as explanations are not conventionally presented in the results section.
The explanation could be moved to the discussion and could include why viraemic HCV would not be treated.
- Thank you for your suggestion. We moved it to Discussion with adding a reference showing the incidence of spontaneous clearance of HCV (line 258-264).
20. Line 154: Sentence does not read well... may missing 'at' after survival rates
- Thank you for your suggestion. We added "at" after survival (line 183).
21. Line 155-160: Move to discussion, sentence also needs rephrasing
- Thank you for your suggestion. We moved it to Discussion, with rephrasing the sentence (line 195-200).
22. Line 163-167: Move to discussion
- Thank you for your suggestion. We moved it to Discussion, with rephrasing the sentence (line 205-210).
23. Figure 1: Table 1 describes the study population at the **age of diagnosis**, while the figure presents survival from **HCC treatment or diagnosis**. Are these populations the same? How did the patients receive HCC treatment before diagnosis?
- Thank you for your comment. Four cases did not receive any treatments for HCC, so that we added the mention in legend of Figure 1.
23. Discussion
Lines 175-178: This seems to be a contradiction of the methods as there was no mention a survey or participation by all infectious disease centres for this to be called a nationwide study. This sentence also provides context and justification for the study, and should probably be in the introduction rather than the discussion.
- Thank you for your suggestion. We moved it to introduction, with rephrasing the sentence (line 102-105).
24. Line 228: I wonder if LT is indeed a feasible and sustainable treatment option for these patients. Globally, there is a huge unmet need of organ donations. In this light, there could be discussion around prevention. Early detection of HCV as well as timely initiation of treatment to prevent HCC is especially important as HCC treatment options for haemophiliac patients are limited, but this is not emphasized.
- Thank you for your comment. Although the LT is recognized as the treatment option even for HIV/HCV coinfection, the prevention of HCC should be much more important, as you mentioned. We added this statement in Discussion (line 262-264).
25. Line 223-224: Further to the above, it needs to be clarified why patients continued to progress to HCC both when pre-DDA treatments were effective and available in Japan, and

in the era of readily available DDAs e.g. a patient diagnosed in 2015. What has been the situation and progress with access to HCV treatment in Japan overall, and for haemophiliacs? Are they a priority population for treatment considering the well-known fact that many were infected iatrogenically through contaminated blood products?

- Thank you for your comment. Honestly, the reason of less adaptation of DAA in Japan might be related to the less interests by HIV physicians, and we described it in Discussion (lines 234-236 and 252-257).

26. Lines 238: Could selection bias be a limitation of the study? It is reported that majority of patients infected with HCV through contaminated blood products in Japan were women, but females are not represented in this study. There is of course a male preponderance of HCC, but the ratio in Japan has also not been discussed in the paper. Did the study identify any specific characteristics to explain why it is men who progress to HCC in Japan?

What was the impact of differing protocols for HCC diagnosis on inclusion in the study?

- Thank you for your comments. Actually, all of the patients in this study were male with haemophilia, so that selection bias might be a limitation. We added the mentions in Discussion (line 282-285).

27. Conclusion

Lines 245-246: The main conclusion is not in line with the aim of the study, and the conclusion in the abstract could also be revised accordingly.

- Thank you for your suggestion. As you pointed out, the aim of the study was to elucidate the outcome of HCC treatment in HIV/HCV coinfecting patients due to unheated blood product in Japan. We changed the title, and updated the conclusion (line 290-292).

Reviewer B

Great and very much needed effort. The sample is expectantly limited, and the conclusions need to be revised accordingly. The choices of therapy are appropriate, but it is not justifiable to imply altered therapies in that setting. It would be valuable to address the screening for HCC necessities for hemophilia patients.

- Thank you for your comments. We believe we responded to Reviewer B comments by responding to Reviewer A comments.