Author's response to reviews

Title: Outcomes and factors influencing survival in cirrhotic cases with spontaneous rupture of hepatocellular carcinoma: a multicenter study

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Author's response to reviews:

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Dear Editors,

We are pleased to submit our revised manuscript entitled “Outcomes and factors influencing the survival in cirrhotic cases with spontaneous rupture of hepatocellular carcinoma: a multicenter study” (Manuscript ID: 1652799316235977) for publication consideration in BMC Gastroenterology.

We have addressed the comments in the revised manuscript in accordance with reviewer’s suggestion. We believe that our paper would be of great interest to the readers of BMC Gastroenterology and look forward to hearing your response.

Sincerely yours,

Hiroyuki Kirikoshi, M.D., Ph.D.
Manuscript ID 1652799316235997 entitled "Outcomes and factors influencing the survival in cirrhotic cases with spontaneous rupture of hepatocellular carcinoma: a multicenter study"

Response to Dr. Jeong Won W. Jang (Reviewer 1)

Thank you very much for your helpful suggestions. Your comments have been addressed in the revised manuscript, which is now greatly improved as a result.

# Major comments 1.

Method: The authors stated that the decision to perform TAE was taken according to the patients’ will. This appears to make no sense; more patients in the conservative group had worsened liver function, in terms of high bilirubin, AST levels, and Child-Pugh scores, more cases of ascites in the conservative group. Given that all of these are found to be associated with early 30-day mortality (even though they are not significant in the multivariate analysis), the discrepancies between patient characteristics in the two groups are a challenging issue for the data interpretation. This could introduce an unintentional bias and perhaps may not strengthen the conclusions from these data.

Comment
Thank you for your comments. We have described the exclusion criteria used in this study in the revised manuscript. We also excluded patients with poor hepatic function in the conservative treatment (ConT) group. The background characteristics of the ConT group (n = 32) and the TAE group (n = 16) in the revised manuscript were not significantly different.

# Major comments 2.

Table 1: The data suggest that some proportion of patients had very decreased hepatic function at baseline. This implies that those were intrinsically not eligible for TAE. It is highly likely that such patients with decompensate liver function could have contributed to confounding factors in the analyses. To substantiate the role of TAE, it is relevant to include only patients with reasonable hepatic function who are eligible for TAE.

Comment
Thank you for your comments. As noted in our response to major comment 1, we have described the exclusion criteria used in this study in the revised manuscript. We also excluded patients with poor hepatic function in the conservative
treatment (ConT) group. We consider that the hepatic function of the ConT group in the revised manuscript was sufficient to enable the performance of TAE. The background characteristics of the ConT and TAE groups in the revised manuscript were not significantly different.

# Major comments 3.
There have been many reports concerning natural course, prognostic factors, and treatment strategy for ruptured HCC. Thus, the overall findings are not new in this field.

Comment
Thank you for your comment. Other groups have reported that hepatic function is very important for the long-term survival of patients with ruptured HCC. However, few previous reports have addressed the notion that the HCC status (i.e., the size of the tumor) is also important for long-term survival, as determined using a multivariate analysis. With regard to this point, our manuscript contains useful information.

# Minor comments 1.
Some previous publications including review articles have indicated that surgical resection (including delayed resection following TAE) for ruptured HCC, if resectable, are a reasonable approach and offer a better, long-term survival. Are there any surgical cases in this study?

Comment
Thank you for your question. None of the patients received surgical treatments (hepatic resection) in our study. The reason for this is that we considered patients with severe ruptured HCC and poor liver function to be incapable of tolerating surgical hepatic resection.

# Minor comments 2.
Results, Page 10: TAE was identified as the only independent predictor of the 30-day survival. These data could be provided by Table.

Comment
Thank you for your suggestion. We have added a new table containing the results of a multivariate analysis showing the influence of various parameters on long-term survival in the revised manuscript.

# Minor comments 3.
Page 6, background: The sentence, “— increasing prevalence of hepatitis B infections”, appears to be inappropriate. With the introduction of HBV vaccination, the prevalence of HBV infection is now decreasing in many countries.

Comment
Thank you for your suggestion. We have removed the phrase, “...increasing
prevalence of hepatitis B virus infections...” from the revised manuscript.

Manuscript ID 1652799316235997 entitled "Outcomes and factors influencing the survival in cirrhotic cases with spontaneous rupture of hepatocellular carcinoma: a multicenter study"

Response to Dr. Sven Wallerstedt (Reviewer 2)

Thank you very much for your helpful suggestions. Your comments have been addressed in the revised manuscript, which is now greatly improved as a result.

# Major comments 1.

The study only comprises cases with cirrhosis, and this should be clearly declared both in the title and in the abstract. Otherwise one can believe that the paper also deals with HCC in non-cirrhotic patients, in which hepatic resection is one of the best treatments. I propose that the word “cirrhotic” should be inserted i) before the word “cases” in the Title, ii) after the word “54” in the Methods part in the Abstract and iii) after the words “treatment strategy” in the Conclusion part in the Abstract.

Comment
Thank you very much for your helpful suggestions. We have inserted the word “cirrhotic” at several places in the revised manuscript.

# Major comments 2.

In this retrospective study some of the 38 patients in the ConT group (or all?) were non-suitable for TAE. Of course it would be of interest to know how many patients that belonged to this group. It is not correct to compare the results of TAE in a group of patients suitable for this procedure with patients who were not suitable for TAE.

Comment
Thank you for your comments. We have described the exclusion criteria used in this study in the revised manuscript. We also excluded patients with poor hepatic function in the conservative treatment (ConT) group. The background characteristics of the ConT group (n = 32) and the TAE group (n=16) in the revised manuscript were not significantly different.

# Major comments 3.

Apparently the patients in the ConT group were sicker than those in the TAE group with a significantly higher Child-Pugh score, including a higher bilirubin value and more frequent ascites. Thus, the two groups differ in a significant way, and then comparisons between the two groups must be performed carefully. For example it should not be surprising that a group of patients with an advanced liver disease had a worse prognosis than patients with a less advanced disease.

Comment
Thank you for your comments. As noted in our response to major comment 1, we
excluded patients with poor hepatic function in the revised manuscript. The background characteristics of the ConT and TAE groups in the revised manuscript were not significantly different. We consider that the hepatic function of the ConT group in the revised manuscript was sufficient to enable the performance of TAE.

# Major comments 4.
The authors divide the initially successfully treated TAE group, comprising of 15 of 16 cases, in two parts according to the size of the largest tumour without any comment of their chose to use 7 cm as a limit.

Comment
Thank you for your comment. The cut-off level for the maximum tumor size used in the statistical analyses was decided based on the median value (7 cm) of the patients. We have added this information to the revised manuscript.

# Major comments 5.
The authors have observed that a bilirubin level exceeding 50 mmol/L is a useful marker of treatment success in patients treated by TAE and report that patients who died within one month had higher bilirubin value than the other patients. This finding was apparently (please, declare if this interpretation is correct) a result from an analysis of the whole material, but it would be of interest to know how many of the TAE cases who had a bilirubin value exceeding 50 mmol/L.

Comment
Thank you for your excellent question. In our study, four patients in the TAE group had a serum bilirubin level that exceeded 50 mmol/L (2.92 mg/dL). The median post-TAE survival time of these four patients was 199 days.

# Major comments 6.
The authors should report if an OLT was performed or not in the follow-up of the patients in the TAE group, which may influence the survival figures. One can for example speculate that TAE makes it possible to get time to find a donor within the first month after rupture.

Comment
Thank you for your comment. Unfortunately, OLTs are difficult to perform in Japan because of a lack of donor organs; consequently, none of the patients underwent an OLT in our study.

# Major comments 7.
The authors should clearly state the limitations of the work.

Comment
Thank you for your suggestion. We have added several new sentences describing the limitations of our study in the revised manuscript (Abstract and Conclusion). As our work was a retrospective study, some inherent limitations
exist.

# Minor comments 1.
Abstract, Results:
a) The sentence “Both the MST …” ought to be eliminated (see point 3 above).
b) In the last sentence the word “initially” should be inserted before the word “successfully” and the words “the size of the tumors as” should be replaced by the words “a size of the largest tumour not exceeding 7 cm was”.

Comment
Thank you very much for your helpful suggestions. We have included the suggested changes in the revised manuscript.

# Minor comments 2.
Abstract, Conclusions:
Please, remove the word “very” (two times).

Comment
Thank you very much for your helpful suggestion. We have included the suggested changes in the revised manuscript.

# Minor comments 3.
Background:
Please, remove the words “, and often have large and/or multiple tumors” in the 5th sentence, since they are unnecessary when talking about advanced HCC.

Comment
Thank you very much for your helpful suggestion. We have included the suggested changes in the revised manuscript.

# Minor comments 4.
Methods.
a) Please, give the number of patients from each of the three hospitals in the 1st para.
b) Please, remove the word “radiological” in the 2nd para.
c) Please, present the degree of the drop of the hemoglobin level to be used as indicator of an intraabdominal bleeding and please, state that if other explanations for this drop had been excluded.
d) Please, remove the words “, and the hepatic function was evaluated” in the 3rd sentence in the 3rd para.
e) Please, explain the reason for using the word “however” in the sentence “An attempt was made …”.
f) I think that the statement of non-suitability for TAE should be inserted in this
part of the manuscript.

Comment
Thank you very much for your helpful suggestions. We have included the changes suggested in (a), (b), and (d) in the revised manuscript.
For (c), we have changed our description of the diagnosis of ruptured HCC according to abdominal puncture in the revised manuscript.
For (e), we have removed this word from the revised manuscript.
For (f), we have described the exclusion criteria in the Methods part of the revised manuscript.

# Minor comments 5.

Results
a) Please, remove the 3rd and 4th sentences in the 2nd para ("The survival …" and "The 30-day …"), since the information is also given below.
b) Please, insert “acute” before “hemorrhage” in the 2nd sentence in the 3rd para.
c) Please, insert the word “initially” before the word “successfully” and the word “inverse” before the word “independent” in the 1st sentence in the 4th para.
d) In the 5th para, which could follow directly after the text in the 4th para I do not understand the figure “62.5%” in the last sentence, since the authors consider just six patients with a tumour >7 cm. Moreover I think that the use of tenths should be avoided when dealing with groups of six and nine patients, respectively.

Comment
Thank you very much for your helpful suggestions. We have included the changes suggested in (a), (b), and (c) in the revised manuscript.
For (d), we are very sorry for this miscalculation. The 12-month survival rate for the patients with a maximum tumor size of # 7 cm was 50.0%. We have corrected this figure in the revised manuscript.

# Minor comments 6.

Discussion
a) In the 1st para the figure “5%” is hard to understand. Please, give an explanation and please, insert the word “initially” before the word “successfully”.
b) Please, remove the word “very” in the last sentence in the 2nd para.
c) In the 4th para the text “(244.8 days …” and the following two sentences, both beginning with “The cumulative survival …” should be removed, since all this information has already been presented in the 3rd para in the Results part.
d) Please remove the three last sentences in the 4th para, since they do not add any new information and are not discussed.
Comment
Thank you very much for your helpful suggestions. We have included the changes suggested in (b), (c), and (d) in the revised manuscript.

For (a), we are very sorry for this miscalculation. We have corrected this figure as “One patient (6.7%)” in the revised manuscript.

# Minor comments 7.
Conclusion
In the 3rd sentence the authors must insert “in cirrhotic patients” after the word “HCC”.

Comment
Thank you very much for your helpful suggestion. We have included the suggested changes in the revised manuscript.

# Minor comments 8.
Figure 1 legend.
The text is too long (all figures are already presented in the text in the Results part) and I recommend the authors to remove it in favour of the following sentence: “Cumulative survival rate in the ConT (conservative treatment) group and in the TAE (transcatheter arterial embolization” group”.

Comment
Thank you very much for your helpful suggestion. We have included the suggested changes in our revised manuscript.

# Minor comments 9.
Figure 2 legend.
The text is too long (all figures are already presented in the text in the Results part) and I recommend the authors to remove it in favour of the following sentence: “Cumulative survival rates in patients according to the size of the largest tumour”.

Comment
Thank you very much for your helpful suggestion. We have included the suggested change in our revised manuscript.

# Minor comments 10.
Table 3.
The authors must be aware of if the figures stand for survival or mortality for the interpretation, which now is difficult, at least considering “Size of the largest tumor :>7cm”.

Comment
Thank you very much for your helpful comment. The cut-off levels for each parameter were decided based on the median levels for all the patients. We have included this information in the Methods section of the revised manuscript.

# Minor comments 11.

Figure 2.
I do not think that the dotted curve is correct. My impression from the figure is that this deals with 5 patients instead of the stated 6 patients.

Comment
Thank you very much for your helpful comment. We have changed this Figure in the revised manuscript.

# Minor comments 12.
Discretionary Revisions
* The affiliation of the authors should be mentioned.
* Non-significant P-values (p>0.05) are unnecessary and could be erased in Tables 1 and 3.

Comment
Thank you very much for your helpful suggestions. We have included the suggested changes in the revised manuscript.

# Minor comments 13.
The word “NS” in Table 1 and Table 3 ought to be explained.

Comment
Thank you very much for your helpful suggestion. We have explained the abbreviation “NS” in the revised manuscript.

Manuscript ID 1652799316235997 entitled "Outcomes and factors influencing the survival in cirrhotic cases with spontaneous rupture of hepatocellular carcinoma: a multicenter study"

Response to Dr. Spiros Delis (Reviewer 3)
Thank you very much for your helpful suggestions. Your comments have been addressed in the revised manuscript, which is now greatly improved as a result.

# Reviewer’s comment 1.
The manuscript and particular the discussion needs to be shortened.

Comment
Thank you for your suggestion. We have shortened the revised manuscript, particularly the Discussion section.
# Reviewer’s comment 2.
The manuscript interesting due to the fairly large cohort of ruptured HCC although the comparison groups are not similar regarding liver function. ConT group seems to have less hepatic reserve compared to TAE group.

Comment
Thank you for your comment. We have described the exclusion criteria used in this study in the revised manuscript. We also excluded patients with poor hepatic function in the conservative treatment (ConT) group. The background characteristics of the ConT group (n = 32) and the TAE group (n = 16) in the revised manuscript were not significantly different.

# Reviewer’s comment 3.
Although all patients died from re-rupture or liver failure in the ConT group, there is no reported effort for rescue TAE in this group of patients who developed re-bleeding. What was the reason?

Comment
Thank you for your question. In the TAE group (n = 16), two patients experienced a re-rupture of their HCC. We performed emergent TAE in these two patients a second time but were unable to rescue them using TAE.

# Reviewer’s comment 4.
There was also not reported any effort for liver resection in patients who eventually survived by TAE. How many patients developed recurrence post TAE and how they were treated during the follow up period before they finally died? Do you use other strategies: such as RF ablation or repeated TAE?

Comment
Thank you for your comments. None of the patients in our study received surgical treatments (hepatic resection). Our strategy for treating the recurrence of HCC after rupture was repeated TA(C)E. However, the hepatic function worsened after HCC rupture in 10 patients; therefore, these patients only received palliative treatment after the first emergent TAE. Four patients received repeated TA(C)E after the first emergent TAE during the follow-up period.

Manuscript ID 1652799316235997 entitled “Outcomes and factors influencing the survival in cirrhotic cases with spontaneous rupture of hepatocellular carcinoma: a multicenter study”

Response to Dr. Kelvin K C Ng (Reviewer 4)
Thank you very much for your helpful suggestions. Your comments have been addressed in the revised manuscript, which is now greatly improved as a result.

# Major comments.
This is a retrospective multicenter study on the survival outcome and the associated prognostic factors in patients with spontaneous ruptured hepatocellular carcinoma (HCC). Transarterial embolization (TAE) was the only independent prognostic factor affecting median survival. One criticism is the way to elaborate the univariate and multivariate analysis of those prognostic factors is not clear. First, the authors need to describe clearly all clinicopathologic factors to be considered for the analysis. Second, the results of univariate analysis needs to be presented and preferably tabulated. Third, the detailed results of multivariate analysis needs to be mentioned. Moreover, due to small number of patients in TAE group, the results of multivariate analysis in this subgroup is not valid.

Comment
Thank you for your suggestions. We have added the results of all the univariate and multivariate analyses as new Tables in the revised manuscript. The cut-off levels of each parameter in the univariate and multivariate analyses were decided based on the median levels for all the patients. Pathological factors were not examined in all the patients; therefore, we could not include statistical analyses comparing such factors in our study. The results of the multivariate analysis for a subgroup of patients (successful initial TAE) were removed because of the small number of patients.

# Minor comment 1.
Table 2 is not necessary since its information is repeated in Fig 1.

Comment
Thank you for your comment. We have removed Table 2 from the revised manuscript.

# Minor comment 2.
Was there any complication after TAE treatment?

Comment
No complications occurred after the emergent TAE procedures for ruptured HCC. Abdominal bleeding caused by a ruptured HCC was not stopped after the performance of emergent TAE in one patient, and this patient died two days later.

# Minor comment 3.
What would be subsequent management protocol after successful TAE treatment?

Comment
Our strategy for the recurrence of HCC after rupture was repeated TA(C)E. However, only four patients received repeated TA(C)E after the first emergent TAE during the follow-up period.