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Title: Risk factors for hepatic decompensation in patients with primary biliary cirrhosis

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Dear Editor,

Thank you very much for the comments from the reviewers. We have revised our manuscript based on the reviewers' suggestions, and highlighted changes in the text for the reviewers' convenience. The comments are addressed below in a point-by-point manner. We hope the changes are satisfactory, and that you will now find the manuscript acceptable for publication.

1. Format has been updated.
2. References and typesetting were corrected.
3. Revision has been made according to the suggestions of the reviewers.

Reviewer 1:

(1) The definition of decompensation in this study should be clarified.

Response: In the current study, hepatic decompensation was been defined as the occurrence of severe functional damage of the liver and one or more complications of liver cirrhosis [1]. We investigated the following features of

decompensation: hypersplenism, ascites, esophageal varices (variceal bleeding), encephalopathy, hypoproteinemia, coagulant function abnormality, and spontaneous bacterial peritonitis. This has now been clarified in the Methods section (Outcome evaluation) on page 7.

(2) It has been reported that patients with PBC show jaundice almost exclusively in stage IV. Although only 11.8% of patients enrolled in this study were at stage III-IV, 29.8% of the enrolled patients showed jaundice. Were the patients with advanced stage often avoided liver biopsy? The authors should explain or discuss on that point.

Response: Compared to patients without liver biopsy, patients who underwent a biopsy had higher levels of TBil and DBil (Table 1). This seems to indicate that patients who underwent a biopsy were at an earlier stage [2]. In addition, more patients with jaundice progressed to hepatic decompensation than their non-jaundiced counterparts in this study (62.3% and 18.2%, $P = 0.005$). Furthermore, more patients presented with jaundice at stage III-IV (53.8% and 25.8%, $P = 0.046$).

Table 1

	With biopsy (n = 110)	Without biopsy (n = 152)	<i>P</i>
TBil (μmol/L)	24.89 ± 30.85	30.33 ± 41.55	0.036
DBil (μmol/L)	12.41 ± 22.70	15.82 ± 30.37	0.044

(3) It has been reported, as the authors mention, that the response to UDCA is associated with the stage of the disease. It is unclear whether

response to UDCA depends on the stage of the patients in this study.

Response: To date, the relationship between histological stage and UDCA response remains controversial. In the current study, the histological stage was found to be a risk factor for UDCA response, which is consistent with previous reports [3-6] (Table 2). However, some studies have reported that there was no difference in histology between biochemical responders and non-responders [7-10].

Table 2

	Responders (n = 70)	Non-responders (n = 39)	<i>P</i>
Histological stage I-II	70/95.9%	27/69.2%	< 0.001

(4) There are many reports demonstrating that the prognosis of PBC patients have been significantly improved after introduction of UDCA treatment. However, the survival rates shown in this study seem to be relatively low. It could be because that large proportion of patients enrolled in this study had advanced disease as shown in the high percentage of jaundice at the time of enrollment. How many percentages of patients with poor prognosis had been treated with UDCA before enrollment? Were the patients with UDCA non-response stopped UDCA treatment? More descriptions are needed to clarify those points.

Response: In the current study, 190 (72.5%) patients received UDCA regularly and responded, while 46 patients (17.6%) took UDCA consistently, but failed to respond to it. Of the latter, 8 patients terminated treatment on

their own. Others (9.9%) did not take UDCA consistently, as prescribed. Only 11 patients were treated with UDCA for a short time before enrollment. We have now clarified this in the Results section (Clinical profiles of the study group at entry) on page 8.

(5) Cox regression analysis of risk factors for hepatic decompensation in Table 5 shows that ALP is a significant factor. Were the levels of ALP correlated with the prognosis of the patients?

Response: Although ALP was found to be a significant predictor in the current model, the HR 95%IC was 1.000-1.002. Therefore, it had a relatively low correlation with survival compared with other factors; its value for this purpose still needs to be confirmed by other large long-term studies.

Reviewer 2:

This paper could not find any reason for any mention to Gama-GT, since it is a great marker for non-declared alcohol ingestion. Another point is the ammonia blood levels that may reveal asymptomatic cases.

Response: In the current study, the level of serum GGT was recorded at baseline (Table 2 in the manuscript) and at each visit. The personal history regarding alcohol intake was recorded and patients with alcoholic liver disease were excluded. In addition, patients with elevated GGT and normal ALP were also excluded.

In case of suspicion of hepatic decompensation in patients, the level of ammonia was measured to evaluate the asymptomatic encephalopathy.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



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