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Dear Editor,
World Journal of Gastroenterology

Thank you for considering our manuscript entitled, "Validation of the albumin-bilirubin (ALBI) score for identifying decompensation risk in patients with compensated cirrhosis." by Navadurong, et al. to be published in *World Journal of Gastroenterology* (Manuscript ID 85133). We have reviewed the comments and considered them carefully. The point-by-point responses to reviewers' and editors' comments are below:

Reviewer #1

I would like to congratulate the authors for conducting this study. The study has been well conducted and the manuscript has been very well written. Only point is that it is already known that ALBI score is a good predictor of decompensation. My few comments are as follows:

Comment 1: The cause of decompensation in the study patients should be added.

Response 1: We thank the reviewer for this suggestion. Among the 17 patients who experienced decompensating events in our study cohort, the most common precipitants of hepatic decompensation in our study cohort were gastrointestinal bleeding (n=8, 47%), followed by infection (n=1, 6%). However, in 8 (47%) of the patients who developed decompensating events, no specific cause of decompensation could be identified.
We have added sentences in the Results section, specifically in the subsection titled " Predictors of decompensation in patients with compensated cirrhosis" as follows:

"Among the 17 patients who experienced decompensating events, the most common precipitants of hepatic decompensation were gastrointestinal bleeding (n=8, 47%), followed by infection (n=1, 6%). However, in 8 (47%) of the patients who developed decompensating events, no specific cause of decompensation could be identified."

Comment 2: How the patients with decompensation were treated?

Response 2: Among the decompensation events observed, 8 patients (47%) experienced variceal bleeding, 5 patients (29.4%) developed ascites, and 4 patients (23.6%) exhibited grade 3 or 4 hepatic encephalopathy. The 8 patients who experienced variceal bleeding received a combination of endoscopic treatment, intravenous octreotide, and antibiotic prophylaxis. Treatment for ascites in the 5 affected patients involved a combination of spironolactone and furosemide, with 1 patient requiring abdominal paracentesis due to tense ascites. All 4 patients with grade 3 or 4 hepatic encephalopathy were treated with lactulose. The patient who experienced decompensation due to infection received intravenous antibiotic therapy.

We have added sentences in the Results section, specifically in the subsection titled " Predictors of decompensation in patients with compensated cirrhosis" as follows:

"The 8 patients who experienced variceal bleeding received a combination of endoscopic treatment, intravenous octreotide, and antibiotic prophylaxis. Treatment for ascites in the 5 affected patients involved a combination of spironolactone and furosemide, with 1 patient requiring abdominal paracentesis due to tense ascites. All 4 patients with grade 3 or 4 hepatic encephalopathy were treated with lactulose.

Additionally, the patient who experienced decompensation due to infection received intravenous antibiotic therapy."

Comment 3: Please also add the information about the survival outcomes of the patients.

Response 3:

We have analyzed the survival outcomes of patients who developed decompensation. Overall survival following the first decompensation was 82.4% at 3 years. The median overall survival of patients developed first decompensation was 29.9 (95% CI: 23.7-36.0) months.

We have added sentences in the Results section, specifically in the subsection titled " Predictors of decompensation in patients with compensated cirrhosis" as follows:

"Overall survival following the first decompensation was 82.4% at 3 years. The median overall survival of patients who developed the first decompensation was 29.9 (95% CI: 23.7-36.0) months."

We also updated sentence in the Methods section, specifically in the subsection titled "Statistical Analysis" as follows:

"Time to decompensation according to baseline ALBI grade and overall survival following the first decompensation were examined by Kaplan-Meier (KM) graphs and compared using the log-rank test."

Reviewer #2

Navadurong et al. presented a retrospective cohort study analyzing the evaluation of ALBI as a predictor of decompensation in patients with compensated liver cirrhosis of various etiologies during a median follow-up of 3 years. The design of the study is well organized. The title, abstract and keywords correspond to the text of the article. Materials and methods are described quite fully and clearly. Correct methods of statistical processing of the obtained data were used. The authors refer appropriately to the recent and current references. The work presented by the authors is an original study performed on sufficient (123 patients) clinical material, which confirms the value of a simple and

accessible ALBI indicator as a predictor of the development of liver cirrhosis decompensation in patients with chronic liver diseases. At the same time, the authors point out the existing limitations of the performed study, a small sample of patients (only 6 patients) of the high-risk group is discussed. Own data are correctly compared with the data presented in the scientific literature. The data obtained by the authors have important clinical significance. In the future, it is desirable to determine the prognostic value of the ALBI index in patients with various nosological conditions (for example, in chronic liver diseases of viral etiology and cholestatic liver damage).

Response to Reviewer #2:

We greatly appreciate the insightful comment from the reviewer. In terms of future perspectives, incorporating additional data on the ALBI score, such as changes in annual ALBI grading or variations in ALBI grades between the compensation and decompensation stages, may provide novel insights for predicting decompensation events. This could potentially offer new information and enhance our understanding of the predictive capabilities of the ALBI score in this context.

Reviewer #3

I am honored to have the opportunity to review this manuscript. This study by Navadurong et al. suggested that the ALBI score accurately identifies decompensation risk at 3 years follow-up in patients with compensated cirrhosis. Overall, the study was explored a novel assessment for decompensation risk in patients with compensated cirrhosis. However, several comments I need to address to make the study more suitable for publication. In 2015, Johnson et al. proposed the albumin-bilirubin (ALBI) grade as a new evidence-based approach for HCC. In 2017, Hiraoka et al. undertook a detailed analysis based on the results of a nationwide survey of 46,681 patients; they proposed that ALBI grade 2 be subdivided into ALBI grades 2a and 2b, correcting the distribution of patients across grades.

Comment 1: ALBI grade was applied for HCC, but the validation of the effectiveness of ALBI grade for cirrhosis was not sufficient. This grade was not invented by the authors. Firstly, the author should verify that albumin and bilirubin could be statistically significant prognostic variables for decompensation cirrhosis. Secondly, the author should construct a new grade by these two parameters and make a new assessment.

Response 1:

We greatly appreciate your kind comment. Nowadays, the application of the ALBI score has been increasingly extended beyond hepatocellular carcinoma (HCC) to chronic liver disease in general. There have been publications demonstrating the strong prognostic value of the ALBI score in cirrhotic patients. In 2018, Hsieh et al. illustrated the ability of the ALBI score to correlate with hepatic venous pressure gradient (HVPG) levels in cirrhotic patients. Similarly, in 2021, Takumi et al. showed that the ALBI score was a significant factor associated with severe portopulmonary hypertension in cirrhotic patients. However, there has been no study evaluating the utility of the ALBI score in predicting the risk of decompensation in patients with compensated cirrhosis. Thus, our study aimed to assess the ability of the ALBI score to identify decompensation risk at a 3-year follow-up in patients with compensated cirrhosis. We chose to utilize the same cut-off points for ALBI grades as in the HCC cohort to facilitate its ease of use for clinicians. Therefore, we did not establish new cut-off points for ALBI grades in our study cohort.

We have incorporated albumin as a predictor of decompensation in patients with compensated cirrhosis, considering that albumin and bilirubin are both included in the calculation of the ALBI score. The updated analysis, including albumin as a factor, is presented in **Table 1**. In the group of compensated cirrhotic patients who experienced an initial decompensation event, univariate analysis revealed that albumin, bilirubin, ALT, ALBI, MELD, ALBI-FIB4, and Child-Pugh score were associated with the occurrence of initial decompensation. In our multivariate analysis, adjusting for age and sex, we included variables only ALBI, MELD, ALBI-FIB4, and Child-Pugh score, as albumin, bilirubin, and ALT are factors used in the calculation of each score. Notably, we observed

that the ALBI score remained independently associated with the occurrence of initial decompensation, as indicated in **Table 1**.

According to the updated analysis for predictors of decompensation in patients with compensated cirrhosis, we have updated sentences in the Results section, specifically in the subsection titled " Predictors of decompensation in patients with compensated cirrhosis" and **Table 2.** Predictors of decompensation in patients with compensated cirrhosis as follows:

"In compensated cirrhotic patients who developed an initial decompensation, albumin, bilirubin, ALT, ALBI, MELD, ALBI-FIB4 and C-P scores were found to be associated with initial decompensation, with an HR of 0.10 (95%CI: 0.03-0.26), 1.21 (95%CI: 1.02-1.43), 1.01 (95%CI: 1.00-1.02), 8.31 (95%CI: 3.48-19.85), 1.11 (95%CI: 1.02-1.21), 2.30 (95%CI: 1.60-3.31), and 1.98 (95%CI: 1.15-3.39), p<0.001, 0.02, 0.01, <0.001, 0.01, <0.001 and 0.01 respectively. In the multivariate analysis, ALBI score remained independently associated with initial decompensation with adjusted HR of 4.18 (95%CI: 1.40-12.53) (p=0.01) (Table 2)."

Table 1. Predictors of decompensation in patients with compensated cirrhosis

Variable	**Univariate**		**Multivariate**	
	Hazard ratio (95% CI)	**P value**	**Adjusted hazard ratio (95% CI)**	**P value**
Age	1.01 (0.97-1.05)	0.47	1.01 (0.97-1.06)	0.56
Male	0.58 (0.22-1.50)	0.26	0.55 (0.18-1.69)	0.29
Creatinine	1.20 (0.83-1.74)	0.31		
Albumin	0.10 (0.03-0.26)	<0.001		
Bilirubin	1.21 (1.02-1.43)	0.02		
AST	1.00 (0.99-1.00)	0.34		
ALT	1.01 (1.00-1.02)	0.01		
Platelet	0.99 (0.98-1.00)	0.27		
INR	1.58 (0.11-22.29)	0.73		

ALBI score	8.31 (3.48-19.85)	<0.001	4.18 (1.40-12.53)	0.01
MELD score	1.11 (1.02-1.21)	0.01	1.07 (0.92-1.24)	0.34
ALBI-FIB4 score	2.30 (1.60-3.31)	<0.001	1.73 (0.82-3.64)	0.15
FIB-4 score	1.02 (0.92-1.13)	0.67		
Child-Pugh score	1.98 (1.15-3.39)	0.01	1.26 (0.61-2.58)	0.54

Comment 2: After conducting a new model, the author should compare it with conventional methods (Child-Pugh et al.). However, ALBI grade belongs to a category of continuous variable, and C-P score belongs to a category of categorical variable. These two cannot be placed in a diagram.

Response 2:

Since we utilized the conventional ALBI grade with the same equation and cut-off points as the HCC cohort, we did not develop a new model for the ALBI score in our study cohort. Instead, we compared the ALBI score with well-established prognostic scoring systems that are currently utilized in clinical practice. This comparison included the MELD score, Child-Pugh score, FIB-4 score, as well as a novel combined prognostic scoring system known as the ALBI-FIB4 score which Indra et al. (2019) had demonstrated the good predictive ability of the ALBI-FIB4 score in identifying the risk of initial decompensation in patients with compensated cirrhosis.

In terms of evaluating the performance of each prognostic score in predicting decompensation at the 3-year follow-up, we focused on analyzing the time-dependent area under the curve (tAUC) for variables including ALBI score, ALBI-FIB4 score, MELD score, Child-Pugh score, and FIB-4 score which are all specifically for continuous variables. We did not analyze the tAUC of Child-Pugh grade or ALBI grade which are specifically for categorical variables

Comment 3: Was there any correlation between ALBI grade and C-P score? A more detailed and clear study design should be provided to outline the number of samples enrolled and the different cohorts distribution (training cohort and validation cohort).

Response 3:

We performed an analysis to investigate the correlation between ALBI grade and Child-Pugh score in our cohort. The results demonstrated a correlation coefficient of 0.28 ($p=0.002$), indicating a very low positive correlation between the two variables. Likewise, when examining the correlation between ALBI score and Child-Pugh score, we observed a correlation coefficient of 0.39 ($p<0.001$), suggesting a low positive correlation between the two variables. Hence, it can be concluded that there is a low correlation between high ALBI grades or ALBI scores and high Child-Pugh scores.

As we utilized the conventional ALBI grade with the same equation and cut-off points as the HCC cohort, we did not develop a new ALBI model in our study cohort. Our study was designed to validate the ability of the ALBI score to identify the risk of decompensation over a 3-year follow-up period in patients with compensated cirrhosis. Therefore, our study cohort consisted of only validation cohort, and we did not include a derivative cohort in our analysis.

Comment 4: Lack of standardization of writing obviously led to poor readability. For example, reference 1 was missing from this manuscript.

Response 4:

We sincerely apologize for the oversight in the reference, and we have now made the necessary corrections. Furthermore, we have thoroughly reviewed the rest of the manuscript and found no additional errors.

Reviewer #4

I have reviewed this manuscript and I believe it is suitable for publication in WJGE. The authors evaluated ALBI score as the predictor of decompensation of patients with compensated liver cirrhosis over the median follow-up of 3 years. According to the results, worsening category of ALBI score was associated with the increased risk of decompensation, with better predictive performance in comparison to other scores that were analyzed here. The only limitation is the small number of patients within the highest

risk category of ALBI score (6 patients), whereas the overall low risk of decompensation could be attributed to the fact that patients with viral hepatitis (more than 50% of all patients in this cohort) were treated by antiviral drugs. This should be commented by the authors in the revised version of the manuscript. My recommendation is to accept the manuscript after the minor revision.

Response to Reviewer #4:

We sincerely appreciate the reviewer's insightful comment. In response, we have conducted an analysis of the etiology of liver disease within each decompensation risk-group. The findings are presented in **Table 2**. Notably, viral hepatitis accounted for 59% of patients in our cohort, all of whom received antiviral treatment resulting in a sustained virological response. Among patients with viral hepatitis, 70.3% were classified as belonging to the low-risk group. We observed a significant increase in the number of patients with viral hepatitis in the low-risk group compared to the middle and high-risk groups (p=0.02). However, there was no statistically significant difference in the prevalence of NASH, alcohol-related liver disease, and AIH among decompensation risk-groups. Consequently, 52% (n=64) of patients in our cohort were categorized as belonging to the low-risk group, while only 4.9% (n=6) were classified as high-risk. This distribution can primarily be attributed to the prevalence of viral hepatitis as the underlying etiology of liver disease in our study population.

We have added sentences in the Results section, specifically in the subsection titled " Decompensation risk stratification based on ALBI grade" in the second paragraph as follows:

"Regarding the etiology of liver disease within each decompensation risk-group, viral hepatitis had a significant increase in the number of patients within the low-risk group compared to the middle and high-risk groups, with 45 (61%), 24 (32.9%), and 4 (5.5%) patients, respectively (p=0.02). However, there was no statistically significant difference in the prevalence of NASH, alcohol-related liver disease, and AIH among the decompensation risk-groups."

We have added sentences in the Discussion section, specifically in the sixth paragraph as follows:

"Viral hepatitis accounted for 59% of patients in our cohort, all of whom received antiviral treatment resulting in a sustained virological response. Among patients with viral hepatitis, 70.3% were classified as belonging to the low-risk group. We observed a significant increase in the number of patients with viral hepatitis in the low-risk group compared to the middle and high-risk groups (p=0.02). Consequently, 52% (n=64) of patients in our cohort were categorized as belonging to the low-risk group, while only 4.9% (n=6) were classified as high-risk. This distribution can primarily be attributed to the prevalence of viral hepatitis as the underlying etiology of liver disease in our study population."

Table 2. Etiology of liver disease within each decompensation risk-group

Etiology of liver disease, n (%)	**Entire cohort**	**Low-risk group**	**Middle-risk group**	**High-risk group**	**p-value**
Viral hepatitis B/C	73 (59)	45 (61.6)	24 (32.9)	4 (5.5)	0.02
NASH	29 (23.6)	15 (51.7)	13 (44.8)	1 (3.5)	1.00
Alcohol	19 (15.4)	8 (42.1)	10 (52.6)	1 (5.3)	0.63
AIH	2 (1.6)	0 (0)	2 (100)	0 (0)	0.28

We believe that our responses and manuscript modifications will prove satisfactory upon review. We thank again the editors and reviewers for their insightful comments.

Sincerely,

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