Journal of Public Health Sciences
Vol. 5, No. 02, pp. 260-268
journal.iistr.org/index.php/JPHS
DOI: 10.56741/IISTR.jphs.001311

The Relationship between the Albumin-Bilirubin Ratio and Frailty in Patients with Liver Cirrhosis

[1]Triyanta Yuli Pramana*, [1]Alwidya Rosyid Akhmad Permana, [1]Fatichati Budiningsih, [2]Hanung Prasetya
Corresponding Author: *typramana@gmail.com
[1] Universitas Sebelas Maret, Surakarta, Indonesia
[2] Politeknik Kesehatan Kementrian Kesehatan Surakarta, Surakarta, Indonesia

ARTICLE INFO

Article history
Received 30 July 2025
Revised 6 September 2025
Accepted 29 April 2026

ABSTRACT

Patients with liver cirrhosis are at risk of impaired liver function, characterized by disturbances in albumin synthesis and bilirubin secretion. The Albumin-Bilirubin (ALBI) score has been reported to be associated with the prognosis of liver cirrhosis patients. This study aimed to analyze the relationship between the ALBI score and frailty in patients with liver cirrhosis. A cross-sectional study was conducted at Dr. Moewardi General Hospital from May to September 2024. A total of 68 patients with liver cirrhosis were included. The dependent variable was frailty, while the independent variable was the ALBI score. Data were collected via a questionnaire and laboratory results, and analyzed using logistic regression. This study found a significant association between a higher ALBI score and frailty in patients with liver cirrhosis. After correcting for data entry errors, the re-analyzed data showed a significant association. A one-unit increase in the ALBI score was associated with a significant increase in the odds of frailty (OR = 13.32; 95% CI = 1.31 to 135.48; p = 0.029). These findings suggest a significant relationship between the ALBI score and frailty in patients with liver cirrhosis, indicating that patients with more severe liver dysfunction (reflected by a higher ALBI score) are more likely to be frail.

Keywords
ALBI Score
Albumin
Bilirubin
Frailty
Liver Cirrhosis Patients

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Introduction

The liver is a vital organ responsible for metabolism and detoxification in the human body, playing a crucial role in biotransformation and the metabolism of various substances [1]. Hepatitis, cirrhosis, and liver cancer represent key and commonly encountered liver diseases. The general pathogenesis of liver disease is as follows: inflammation and other pathogenic factors lead to sustained liver injury [2], which in turn activates hepatic stellate cells (HSCs) and results in excessive deposition of extracellular matrix [3]. Patients with chronic hepatitis are at high risk of progressing to liver fibrosis, cirrhosis, and even life-threatening liver cancer, which poses a significant public health concern [4].

According to the World Health Organization, at least 296 million people worldwide are infected with the chronic hepatitis B virus (HBV), and the number of deaths caused by cirrhosis and hepatocellular carcinoma due to HBV infection is approximately 820,000 [5]. Assessing the severity and prognosis of patients with liver cirrhosis is essential for determining appropriate management strategies. Several scoring systems have been employed, such as the Child-Pugh Score and the Model for End-Stage Liver Disease (MELD). However, both systems have limitations, primarily due to the inclusion of subjective parameters or variables that do not fully reflect pure hepatic function [6].

As an alternative, the Albumin-Bilirubin (ALBI) score was developed to provide a more objective assessment of liver function using two readily available laboratory parameters: serum albumin and bilirubin levels [7], [8]. The ALBI score offers a quantitative approach without subjective components and has been validated in various studies, particularly among patients with hepatocellular carcinoma (HCC) [9], [10]. Recent research, however, has shown that the ALBI score also holds important prognostic value in cirrhotic patients without cancer, including in evaluating the risk of complications, the need for medical interventions, and predicting mortality [11].

Considering that liver cirrhosis is a multisystem condition affecting patients' nutritional status, immune function, and physiological reserves, the use of the ALBI score as a clinical assessment tool has become increasingly relevant. Therefore, a deeper understanding of the role of the ALBI score in risk stratification and therapeutic planning for cirrhotic patients is essential to improving the quality of care and clinical outcomes. This study aims to analyze the relationship between the albumin-bilirubin (ALBI) ratio and frailty in patients with liver cirrhosis.

Material and Methods

A. Research Design

This was a cross-sectional study conducted at Dr. Moewardi Regional General Hospital (RSUD) from May to September 2024 [12]. The study included a total of 68 patients diagnosed

with liver cirrhosis who were undergoing treatment at the hospital. A total sampling method was used, including all patients who met the following criteria: confirmed diagnosis of liver cirrhosis by a gastroenterologist based on imaging (ultrasound, CT, MRI) or liver biopsy, age 18 years or older, and providing written informed consent. Patients were excluded if they had a recent (< 1 month) history of acute infection, severe decompensation (e.g., active variceal bleeding, refractory ascites requiring paracentesis within 48 hours of assessment), or were unable to participate in the frailty assessment due to cognitive impairment or severe illness [13].

B. Variables and Measurements

1. Independent Variable

The Albumin-Bilirubin (ALBI) score, a quantitative measure of liver function, was used as the independent variable. It was calculated using the formula:

$$\text{ALBIscore} = (0.66 \times \log10\text{bilirubin}(\mu\text{mol/L})) + (-0.085 \times \text{albumin (g/L)}) \quad (1)$$

Bilirubin was converted from mg/dL to µmol/L by multiplying by 17.1, and albumin was converted from g/dL to g/L by multiplying by 10. Laboratory data were obtained from the most recent test results available, within 48 hours of the frailty assessment.

2. Dependent Variable

Frailty was the dependent variable, measured using the Fried Frailty Index (FFI). The FFI assesses five components: unintentional weight loss, self-reported exhaustion, low physical activity, slowness, and weakness. Each component was assessed as present or absent (1 or 0, respectively). The total score ranged from 0 to 5. Based on standard FFI criteria, patients were categorized as non-frail (score of 0), pre-frail (score of 1-2), or frail (score of 3-5). For the primary logistic regression analysis, the frailty variable was dichotomized into non-frail/pre-frail (0) and frail (1) to examine the primary association with the ALBI score. A sensitivity analysis using all three categories (robust, pre-frail, and frail) was also conducted.

C. Statistical Analysis

All analyses were performed using STATA version 13. Descriptive statistics were presented as frequencies and percentages for categorical variables and means and standard deviations (SD) for continuous variables. A simple logistic regression model was used to assess the unadjusted association between the continuous ALBI score and the dichotomized frailty outcome. Due to the high potential for confounding, a multivariable logistic regression model was also performed, adjusting for key confounders including age, sex, Body Mass Index (BMI), and the presence of diabetes. The results are presented as odds ratios (OR) with 95% confidence intervals (CI) and p-values. The negative log-likelihood was correctly reported as a

positive value. Sensitivity analyses were conducted to ensure the robustness of the findings, including using different cutoffs for frailty and re-analyzing the data after correcting for implausible albumin values.

D. Ethical Considerations

Ethical approval for the study was obtained from the Ethics Committee of Dr. Moewardi Hospital (Number: 1725/VII/HREC/2024). Written informed consent was obtained from all participants. All patient information was kept confidential.

Results

A. Sample Characteristics

After correcting for data entry errors in the albumin values and recalculating the ALBI scores, the descriptive statistics were updated. The physiologically impossible maximum albumin value of 14.60 g/dL was identified as a transcription error and corrected. The final sample size was 68 patients.

Table 1. Characteristics of Subjects by Sex

Characteristic	Frequency (n)	Percentage (%)
Sex		
• Male	56	82.35
• Female	12	17.65
Frailty Status		
• Non-frail	23	33.82
• Frail	45	66.18

Table 2. Characteristics of Subjects (Continuous Data)

Characteristic	N	Mean	SD	Min	Max
Age (years)	68	49	7.90	23	59
Body Mass Index (kg/m^2)	68	22.69	04.09	14.71	40.79
Albumin (g/dL)	68	3.77	0.54	2.10	4.90
Bilirubin (mg/dL)	68	1.82	2.25	0.45	16.70
ALBI Score	68	-2.22	0.85	-3.52	0.95
Frailty Score	68	2.88	1.21	0	5

B. Simple and Multivariable Logistic Regression Analysis

The relationship between the ALBI score and frailty was re-analyzed using logistic regression. A higher ALBI score was significantly associated with a greater likelihood of being frail.

Table 3. Results of Simple and Multivariable Logistic Regression Analysis

Independent Variable	OR	95% CI	p
Simple Logistic Regression			
ALBI Score	13.32	1.31 – 135.48	29
Multivariable Logistic Regression			
ALBI Score	12.55	1.10 – 143.01	42
Age	01.05	0.98 – 1.13	121
Sex (Female vs Male)	1.56	0.45 – 5.43	487
BMI	0.92	0.81 – 1.04	188

The reported odds ratio for the ALBI score represents the change in odds of being frail for every one-unit increase in the ALBI score. The very wide confidence intervals indicate imprecision in the estimate, likely due to the small sample size.

Discussions

This study provides preliminary evidence of a significant association between a higher Albumin-Bilirubin (ALBI) score and an increased likelihood of frailty in patients with liver cirrhosis [14]. Our findings suggest that a one-unit increase in the ALBI score is associated with a more than 13-fold increase in the odds of a patient being frail, a relationship that remained statistically significant even after adjusting for age, sex, and BMI in a multivariable model [15]. This result aligns with established pathophysiological principles, as the ALBI score, derived from albumin and bilirubin levels, directly reflects the liver's synthetic function and excretory capacity. A declining liver function, as indicated by a higher ALBI score, is intrinsically linked to systemic derangements that predispose patients to frailty [16], [17].

The ALBI score's utility in this context stems from its ability to provide a quantitative, objective measure of liver reserve. Unlike older systems like the Child-Pugh score, which relies on subjective clinical parameters such as the degree of ascites and encephalopathy, the ALBI score is based solely on laboratory values [18]. A lower albumin level, a key component of the score, is a robust indicator of malnutrition and impaired hepatic protein synthesis, both of which are central to the development of sarcopenia and generalized weakness—two core components of frailty [19]. Similarly, elevated bilirubin levels reflect a compromised excretory function, which is often a hallmark of advanced liver disease. The combination of these two parameters provides a more nuanced and objective window into the extent of liver damage, allowing for a better prediction of a patient's functional status and resilience [20].

Despite these compelling findings, it is crucial to interpret the results within the context of the study's significant methodological limitations. The most critical of these is the cross-sectional design. This study captures a single snapshot in time, allowing us to identify an association but precluding any conclusion about causality. While a deteriorating liver function (higher ALBI score) can lead to frailty, the reverse may also be true. Frailty, often driven by chronic inflammation, poor nutritional intake, and a sedentary lifestyle, can exacerbate liver dysfunction [21]. This bidirectional relationship is a fundamental challenge in cross-sectional research on complex syndromes. A longitudinal study, following a cohort of patients over time, would be necessary to determine if a rising ALBI score precedes the onset of frailty, thereby establishing a temporal relationship that strengthens the case for causality.

Furthermore, the imprecision of the odds ratio (OR), as evidenced by the extremely wide 95% confidence interval (CI) of 1.31 to 135.48, is a major concern. The OR of 13.32, while statistically significant, is highly unstable. A wide CI suggests that the true effect could be as

small as a 31% increase in risk or as large as a 135-fold increase, rendering the point estimate clinically unreliable [22]. This imprecision is a direct consequence of the small sample size of 68 patients. A larger sample would provide more statistical power, leading to a narrower CI and a more stable, generalizable estimate of the effect. This limitation underscores the need for replication in a larger cohort [23].

The potential for uncontrolled confounding is another substantial limitation. Frailty and liver dysfunction are intertwined with a host of other clinical factors, including the etiology of cirrhosis (e.g., alcohol, viral hepatitis), the presence of decompensating events (e.g., ascites, hepatic encephalopathy), and comorbidities such as diabetes and cardiovascular disease. The multivariable model in this study only adjusted for age, sex, and BMI [24]. The omission of these other crucial variables could lead to a biased estimate of the relationship between the ALBI score and frailty. For instance, an individual with severe alcoholic cirrhosis may have both a high ALBI score and significant frailty, but their frailty may be largely driven by poor nutrition and muscle wasting related to chronic alcoholism, not solely by liver function as measured by ALBI. Future research must incorporate these variables into a more comprehensive statistical model to isolate the independent effect of the ALBI score.

Finally, the measurement of frailty in this study, while based on a standardized tool, warrants further discussion. The Fried Frailty Index (FFI) was originally developed and validated for a geriatric population. Its application in a relatively younger (mean age 49) and chronically ill population, like liver cirrhosis patients, may not be entirely appropriate. The Liver Frailty Index (LFI), a tool specifically designed and validated for this patient population, incorporates measures like grip strength and chair stands that are more relevant to the physical decline seen in liver disease. The decision to dichotomize the FFI score into two categories (non-frail and frail) also simplifies a complex, continuous spectrum of physical decline. This categorization may have led to a loss of valuable information and may not accurately reflect the "pre-frail" state, which is a critical window for clinical intervention.

This study uncovers an important association between the ALBI score and frailty; its findings should be considered a hypothesis-generating exercise rather than a definitive conclusion. The results highlight the potential utility of the ALBI score as a simple and objective screening tool for frailty in patients with cirrhosis. However, due to significant methodological limitations—including the cross-sectional design, small sample size, and unaddressed confounding factors—the clinical application of these findings should be approached with caution. Future research with a longitudinal design, a larger and more diverse patient population, and the inclusion of a comprehensive set of clinical and laboratory variables is imperative to validate these preliminary findings and to fully understand the intricate relationship between liver dysfunction and frailty in this vulnerable patient population.

Conclusion

This cross-sectional study demonstrates a significant association between higher Albumin-Bilirubin (ALBI) scores and the presence of frailty in patients with liver cirrhosis. The findings suggest that the ALBI score, a simple and objective measure of liver function, may be a useful indicator for identifying patients at greater risk of frailty. This observed association underscores the critical link between declining liver synthetic and excretory function and the development of frailty, a syndrome characterized by diminished physiological reserve. The results highlight the importance of incorporating functional assessments into the routine clinical management of patients with cirrhosis, particularly for those showing evidence of worsening liver function.

While this study provides important preliminary evidence, it also emphasizes the need for further research to address its limitations. Prospective longitudinal studies are needed to establish whether a rising ALBI score precedes the onset of frailty, clarifying the temporal relationship and supporting causal inference. Future studies should employ multivariable models that account for potential confounders, including cirrhosis etiology (e.g., alcohol, viral hepatitis), decompensating events (e.g., ascites, encephalopathy), nutritional status, and comorbidities such as diabetes. Controlling for these factors will allow for a more precise and unbiased assessment of the independent relationship between the ALBI score and frailty.

Given the wide confidence intervals observed in this study, larger multicenter cohorts are necessary to validate these findings and generate results that are generalizable to a broader patient population. Additionally, comparing the ALBI score with other frailty assessment tools, such as the Liver Frailty Index (LFI), could help determine the most practical and effective method for frailty screening in patients with cirrhosis. Ultimately, future research should explore the clinical utility of the ALBI score in guiding patient care. Investigating whether routine frailty screening using ALBI can inform targeted interventions—such as nutritional support or physical therapy—has the potential to improve patient outcomes, reduce hospitalizations, and enhance quality of life.

Limitations

This study has several important limitations that must be acknowledged. First, its cross-sectional design prevents the establishment of causality, as the temporal relationship between ALBI score and frailty cannot be determined, and the bidirectional interplay between the two remains unresolved. Second, the small sample size of 68 patients resulted in wide confidence intervals around the odds ratio, limiting the stability and generalizability of the findings. Third, the multivariable analysis adjusted only for age, sex, and BMI, leaving out other relevant confounders such as cirrhosis etiology, decompensating events, nutritional status, and comorbidities, which may have biased the observed association. In addition, frailty was

measured using the Fried Frailty Index (FFI), a tool originally validated in geriatric populations, which may not fully capture the nuances of frailty in cirrhotic patients, particularly the pre-frail state that is clinically significant. These methodological limitations indicate that the findings should be interpreted cautiously and considered exploratory rather than conclusive.

Conflict of Interest

The authors declare no conflict of interest.

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Authors



Triyanta Yuli Pramana is a medical professional and researcher affiliated with the Gastroenterohepatology Division of Internal Medicine at Universitas Sebelas Maret, Indonesia. His academic interests focus on gastroenterology, hepatology, internal medicine, and clinical research development. He has actively contributed to scientific publications and interdisciplinary healthcare studies. In addition to academic activities, he is involved in medical education and collaborative research initiatives aimed at improving healthcare quality and evidence-based clinical practice in Indonesia. (email: typramana@gmail.com).



Alwidya Rosyid Akhmad Permana is affiliated with the Faculty of Medicine, Universitas Sebelas Maret, Indonesia, specializing in Internal Medicine. His academic and professional interests include clinical medicine, patient-centered healthcare, and medical research. He has participated in various collaborative studies related to disease management and healthcare innovation. Through his involvement in academic and clinical settings, he contributes to advancing medical knowledge and supports integrating evidence-based approaches into healthcare services and medical education. (email: alwidyarosyid@gmail.com).



Fatichati Budiningsih is a lecturer and researcher in the Geriatric Division of Internal Medicine at Universitas Sebelas Maret, Indonesia. Her expertise centers on geriatric medicine, elderly healthcare management, and chronic disease prevention among aging populations. She has been actively engaged in academic research, community health programs, and interdisciplinary collaborations addressing elderly wellbeing. Her scholarly contributions emphasize improving the quality of life for older adults through comprehensive healthcare approaches, preventive strategies, and evidence-based geriatric medical services in Indonesia. (email: fbudiningsih1972@gmail.com).



Hanung Prasetya is affiliated with the Study Program in Acupuncture at Politeknik Kesehatan Kementrian Kesehatan Surakarta, Surakarta, Indonesia. His academic interests include acupuncture therapy, complementary medicine, public health, and integrative healthcare practices. He has contributed to research and educational activities related to alternative and traditional medical approaches. Through academic collaboration and professional engagement, he supports the development of evidence-based complementary medicine and promotes innovative healthcare practices within Indonesia's medical and health education sectors. (email: hanungprasetya168@gmail.com).