ORIGINAL ARTICLE

The Association between Myostatin and Sarcopenia in Liver Cirrhosis

Komang Agus Wira Nugraha,[1] I Ketut Mariadi,[1] I Gusti Agung Suryadarma,[2] Gde Somayana[1] and Cokorde Istri Yuliandari Krisnawardani Kumbara[3]

[1]*Gastroenterohepatology Division, Internal Medicine Department, Faculty of Medicine, Udayana University/Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar, Bali, Indonesia*
[2]*Internal Medicine Department, Surya Husadha Hospital, Denpasar, Bali, Indonesia*
[3]*Gastroenterohepatology Division, Internal Medicine Department, Faculty of Medicine, Udayana University/Udayana University Hospital, Badung, Bali, Indonesia*

ABSTRACT

Background. Sarcopenia is highly prevalent in patients with liver cirrhosis and contributes to decreased quality of life, increased morbidity, and mortality. The role of myostatin in cirrhosis-related sarcopenia remains controversial but may represent a potential therapeutic target.

Objective. This study aimed to investigate the association between serum myostatin levels and sarcopenia in patients with liver cirrhosis.

Methods. A cross-sectional study was conducted with 80 patients diagnosed with liver cirrhosis at Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar, Bali, Indonesia. Serum myostatin levels (ng/L) were measured using an ELISA technique. Sarcopenia was diagnosed based on the 2019 Asian Working Group for Sarcopenia (AWGS) consensus. Elevated myostatin levels were defined as values above the median. Bivariate and multivariate analyses were performed to assess associations between myostatin, cirrhosis severity, and sarcopenia.

Results. The severity of cirrhosis (CTP B and C) was associated with elevated myostatin levels (PR = 2.046; 95% CI: 1.310–3.193; p = 0.002). Bivariate analysis demonstrated that elevated myostatin (PR = 2.178; 95% CI: 1.370–3.461; p <0.001), CTP B and C (PR = 1.818; 95% CI: 1.223–2.701; p = 0.004), ascites (PR = 1.606; 95% CI: 1.110–2.324; p = 0.034), and malnutrition (PR = 1.806; 95% CI: 1.242–2.626; p = 0.004) were associated with sarcopenia. In multivariate analysis, only elevated serum myostatin remained significantly associated with sarcopenia (AOR = 4.273; 95% CI: 1.557–11.724; p = 0.005).

Conclusion. Elevated serum myostatin levels are strongly associated with sarcopenia in patients with liver cirrhosis. Cirrhosis severity is also linked to higher myostatin levels, suggesting a potential role for myostatin-targeted interventions in sarcopenia management.

Keywords: myostatin, sarcopenia, liver cirrhosis

Corresponding author: Komang Agus Wira Nugraha
Gastroenterohepatology Division
Internal Medicine Department
Faculty of Medicine
Udayana University/Prof. Dr. I.G.N.G. Ngoerah General Hospital
Jl. Diponegoro, Dauh Puri Klod, Kec. Denpasar Bar.,
Kota Denpasar, Bali 80113, Indonesia
Email: nugrahawira03@gmail.com

INTRODUCTION

Liver cirrhosis is a late-stage, progressive liver fibrosis characterized by distortion of liver architecture. Worldwide, liver cirrhosis is a leading cause of liver-related mortality, accounting for over 1.32 million deaths in 2017, including 440,000 female and 883,000 male deaths.[1] Mortality in cirrhotic patients arises from various complications such as ascites, hepatic encephalopathy, variceal bleeding, susceptibility to infection, renal dysfunction, hepatocellular carcinoma (HCC), and sarcopenia.[2-4] Among these, sarcopenia is the most common yet often remains underrecognized by clinicians.[3]

Sarcopenia is a syndrome characterized by progressive and generalized loss of muscle mass and strength.[5] Its prevalence in patients with liver cirrhosis ranges from 40–70%, surpassing the prevalence of other complications such as variceal bleeding, refractory ascites, and HCC. Sarcopenia increases the risk of infections, including sepsis-related mortality.[6] Moreover, the survival rate of cirrhotic patients with sarcopenia is significantly lower than that of patients without sarcopenia.[7]

Given the clinical implications of sarcopenia, identifying effective management strategies is crucial. Despite various approaches developed based on the multifactorial pathogenesis of sarcopenia, current strategies have not effectively improved sarcopenia in cirrhotic patients.[6,8] A promising future strategy is targeting myostatin for therapeutic intervention.

Myostatin is a member of the transforming growth factor β (TGF-β) superfamily and the myokine family, as it is primarily secreted by skeletal muscle. Hyperammonemia in liver cirrhosis triggers increased myostatin expression, and higher degrees of liver damage correlate with higher myostatin levels.[9-11] Elevated myostatin inhibits the mammalian target of rapamycin 1 (mTORC1) pathway, reducing muscle protein synthesis and contributing to sarcopenia.[12]

Although several studies have linked myostatin to sarcopenia, the evidence remains controversial. For example, Bekki et al. reported no significant difference in myostatin levels between cirrhotic patients with and without muscle atrophy in a sample of 39 subjects.[13]

Therefore, this study aims to clarify the role of myostatin in sarcopenia among patients with liver cirrhosis. In addition to enriching potential therapeutic approaches, it seeks to resolve existing controversies by evaluating the association between myostatin and sarcopenia while accounting for relevant confounding variables.

METHODS

Study Design, Study Area, and Period

This cross-sectional study was conducted at Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar, Bali, from September to November 2021. The study protocol was approved by the Ethics Committee of the Medical Faculty, Udayana University, Denpasar, Bali (No. 2252/UN14.2.2.VII.14/LT/2021).

Study Participants and Sample Size

The study population consisted of liver cirrhosis patients at Prof. Dr. I.G.N.G. Ngoerah General Hospital. Patients meeting the inclusion and exclusion criteria comprised the study sample. The minimum required sample size, calculated for a 95% confidence level and 5% precision, was 78 participants. Consecutive sampling was used to enroll participants.

Inclusion criteria were hospitalized or outpatient liver cirrhosis patients aged ≥18 years, irrespective of etiology. Exclusion criteria included stroke, malignancy, pregnancy, and corticosteroid use. Liver cirrhosis was diagnosed based on anamnesis, physical examination, laboratory tests, with or without abdominal ultrasound findings, or transient elastography alone. All participants provided informed consent prior to enrollment.

Participant Flow

A total of 110 potential participants were assessed for eligibility, and 80 were included in the study analysis (Figure 1).

Data Collection

Five milliliters (5 mL) of venous blood were collected in Vaculab non-EDTA tubes. Serum myostatin levels were measured using an ELISA immunoassay and reported in ng/L. The median myostatin level was used as the cut-off, categorizing participants into normal (< median) or elevated (≥ median) serum myostatin.

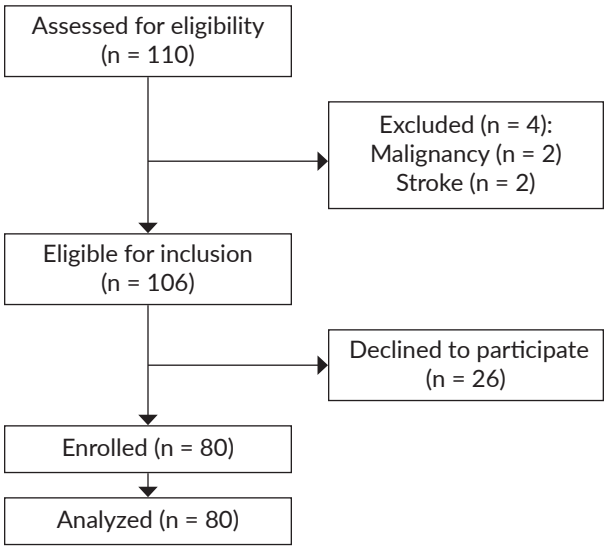

Figure 1. ***Participant Flow Diagram.*** This flow diagram displays the progression of participants through assessment of eligibility, enrolment, and analysis.

Sarcopenia was diagnosed according to the Asian Working Group for Sarcopenia (AWGS) 2019 consensus, defined as low muscle mass accompanied by low muscle strength and/or low physical performance.[14] Muscle mass was assessed using bioelectrical impedance analysis (BIA) and expressed as the skeletal muscle index (SMI, kg/m^2). SMI was calculated using the formula by Jansen et al., as muscle mass (kg) divided by height squared (m^2), with low SMI defined as <7.0 kg/m^2 for males and <5.7 kg/m^2 for females.[15] Muscle strength was measured by handgrip dynamometry (<28 kg for males, <18 kg for females), and physical performance was assessed via a 6-meter walk test (<1.0 m/s). Sarcopenia was confirmed when participants exhibited low SMI along with low muscle strength and/or low physical performance. All measurements were performed by the same examiner to reduce measurement bias.

Confounding variables included age, gender, ascites, Child-Turcotte-Pugh (CTP) score, chronic kidney disease (CKD), diabetes mellitus (DM), and malnutrition. Malnutrition was assessed using the Subjective Global Assessment (SGA) questionnaire, while other confounding data were obtained from medical records.

Table 1. Baseline Characteristics

Variables	Descriptions (n = 80)
Age (years) ± SD*	50.55 ± 11.29
Gender, n (%)	
Male	58 (72.5)
Female	22 (27.5)
Etiology of liver cirrhosis, n (%)	
Hepatitis B virus	64 (80.0)
Hepatitis C virus	14 (17.5)
Others	2 (2.5)
CTP score, n (%)	
CTP A	49 (61.2)
CTP B	16 (20.0)
CTP C	15 (18.8)
Ascites, n (%)	
Yes	17 (21.2)
No	63 (78.8)
CKD, n (%)	
Yes	16 (20.0)
No	64 (80.0)
DM, n (%)	
Yes	7 (8.8)
No	73 (91.2)
Malnutrition, n (%)	
Yes	26 (32.5)
No	54 (67.5)
BMI (kg/m^2) ± SD*	23.59 ± 3.94
SMI (kg/m^2)†	6.47 (3.38-26.12)
Muscle strength (kg)†	24.70 (11.70-48.30)
Myostatin (ng/L)†	45.265 (0.44-1156.67)
Sarcopenia, n (%)	
Yes	43 (53.8)
No	37 (46.2)

** = mean, † = median*

Data Analysis

Descriptive statistics were used to summarize participant characteristics. Bivariate associations between myostatin, confounding variables, and sarcopenia were evaluated using the Chi-Square test. Multivariate logistic regression was performed to assess the association between elevated myostatin and sarcopenia after adjusting for confounding variables. Statistical analyses were performed using SPSS version 25.0.

RESULTS

Baseline Characteristics

The study included 80 patients with liver cirrhosis, comprising 58 males (72.5%) and 22 females (27.5%), with a mean age of 50.55 ± 11.29 years. The Kolmogorov-Smirnov test indicated that SMI, muscle strength, and myostatin were not normally distributed (p <0.001). Baseline characteristics of the participants are summarized in Table 1.

Bivariate Association between the CTP Score and Myostatin

Myostatin levels were categorized using the median value (45.265 ng/L) as the cut-off: normal (<45.265 ng/L) and high (≥45.265 ng/L). A significant association was found between higher CTP scores (B and C) and elevated myostatin levels (PR = 2.046, 95% CI: 1.310–3.193, p = 0.002) (Table 2).

Bivariate Association between Myostatin, Confounding Variables, and Sarcopenia

Bivariate analysis revealed that high myostatin levels were significantly associated with sarcopenia: 29 of 39 patients (74.4%) with high myostatin had sarcopenia versus 14 of 41 patients (34.1%) with normal myostatin (PR =

Table 2. Bivariate Analysis between CTP Score and Myostatin

Variable	Myostatin		PR	CI 95%	*p* value
	High (n=39), n (%)	Normal (n=41), n (%)			
CTP score					
CTP B and C	22 (71.0)	9 (29.0)	2.046	1.310-3.193	0.002*
CTP A	17 (34.7)	32 (65.3)			

** = significant*

2.178, 95% CI: 1.370–3.461, p <0.001). Other variables significantly associated with sarcopenia included CTP B/C scores, presence of ascites, and malnutrition (Table 3).

Multivariate Association between Myostatin, Confounding Variables, and Sarcopenia

Multivariate logistic regression was performed including variables with p <0.25 in bivariate analysis. After adjusting for confounding factors, elevated myostatin remained independently associated with sarcopenia (AOR = 4.273, 95% CI: 1.557–11.724, p = 0.005). Other variables, including CTP score, ascites, DM, malnutrition, and gender, were not statistically significant in the final model (Table 4).

DISCUSSION

In both bivariate and multivariate analyses, elevated myostatin consistently showed a significant association with sarcopenia. This finding aligns with the study by Nishikawa et al., which reported a significant negative correlation between myostatin levels and psoas muscle index (PMI).[11] The median PMI was lower in cirrhotic patients with high myostatin compared to those with low myostatin.

Qiu et al. demonstrated that hyperammonemia in liver cirrhosis can increase myostatin expression.[16] Elevated ammonia levels correlate with higher myostatin expression and reduced muscle mass. Exposure of myotubes to

Table 3. Bivariate Analysis between Myostatin, Confounding Variables, and Sarcopenia

Variables	Sarcopenia		PR	CI 95%	*p* value
	Yes (n=43), n (%)	No (n=37), n (%)			
Myostatin					
High	29 (74.4)	10 (25.6)	2.178	1.370-3.461	<0.001*
Normal	14 (34.1)	27 (65.9)			
Age					
≥60 years	10 (58.8)	7 (41.2)	1.123	0.707-1.783	0.636
<60 years	33 (52.4)	30 (47.6)			
Gender					
Male	28 (48.3)	30 (51.7)	0.708	0.479-1.046	0.111
Female	15 (68.2)	7 (31.8)			
CTP score					
CTP B and C	23 (74.2)	8 (25.8)	1.818	1.223-2.701	0.004*
CTP A	20 (40.8)	29 (59.2)			
CKD					
Yes	9 (56.3)	7 (43.8)	1.059	0.649-1.728	0.823
No	34 (53.1)	30 (46.9)			
DM†					
Yes	2 (28.6)	5 (71.4)	0.509	0.155-1.670	0.240
No	41 (56.2)	32 (43.8)			
Ascites					
Yes	13 (76.5)	4 (23.5)	1.606	1.110-2.324	0.034*
No	30 (47.6)	33 (52.4)			
Malnutrition					
Yes	20 (76.9)	6 (23.1)	1.806	1.242-2.626	0.004*
No	23 (42.6)	31 (57.4)			

*PR = prevalence ratio, * = significant, † = Fisher Exact test*

Table 4. Multivariate Analysis by Logistic Regression Test (backward method)

Variables	Step 1			Step 5		
	AOR	CI 95%	*p* value	AOR	CI 95%	*p* value
CTP score (B and C)	1.897	0.432-8.332	0.396	2.790	0.966-8.056	0.058
Myostatin (High)	4.479	1.498-13.389	0.007	4.273	1.557-11.724	0.005*
Ascites (Yes)	1.660	0.318-8.655	0.548	-	-	-
DM (Yes)	0.218	0.027-1.738	0.150	-	-	-
Malnutrition (Yes)	1.268	0.284-5.652	0.755	-	-	-
Gender (Male)	0.532	0.166-1.707	0.289	-	-	-

*AOR = adjusted odd ratio, * = significant*

ammonium acetate increases myostatin mRNA and protein expression, likely via activation of the NF-κB transcription factor. Myostatin affects gene transcription involved in skeletal muscle precursor proliferation and differentiation, as well as the degradation pathway of mature myofiber protein.[17] Additionally, myostatin inhibits mTORC1, reducing muscle protein synthesis and increasing autophagy.[12]

Myostatin-mediated muscle autophagy involves autophagosome formation and upregulation of autophagy-related genes such as ATG-4B, ULK-2, and GARAPL1. It also prolongs muscle degradation through increased expression of the MuRF-1 gene, which is involved in proteasomal degradation.[18] Latres et al. further demonstrated in vivo that myostatin is a negative regulator of muscle mass.[19] Administration of a myostatin antibody (REGN1033) in mice increased muscle fiber area and isometric force, preventing muscle atrophy and loss of strength. These studies highlight the major role of myostatin in regulating satellite cell activation and myofiber fusion.

Conversely, our findings differ from Bekki et al., who reported no significant correlation between myostatin and SMI.[13] This discrepancy may be due to the small sample size (n = 39) and inclusion of patients with hepatocellular carcinoma (HCC), which independently affects muscle mass.

While no confounding variables were statistically significant in multivariate analysis, several showed associations with sarcopenia in bivariate analysis. Higher CTP scores were associated with sarcopenia, consistent with Tantai et al., who reported a higher prevalence of sarcopenia in CTP C patients compared to CTP A or B.[20] The mechanism likely involves myostatin, as progressing liver damage increases ammonia levels, which then upregulates myostatin, contributing to sarcopenia.[12,21] In our study, bivariate analysis confirmed that CTP B/C scores were significantly associated with elevated myostatin (PR = 2.046, 95% CI: 1.310–3.193, p = 0.002). Controlling liver damage may therefore help prevent increases in myostatin levels.

Malnutrition was also associated with sarcopenia in bivariate analysis. Malnutrition reduces substrates for muscle synthesis, contributing to sarcopenia.[22] In cirrhotic patients, protein malnutrition can decrease skeletal muscle mass and cause hypoalbuminemia.[23] Inadequate intake and absorption of macro- and micronutrients further exacerbate sarcopenia risk.[24] Hayashi et al. similarly reported that insufficient nutritional intake negatively affects sarcopenia.[25]

Contrary to findings in the general population, age was not associated with sarcopenia in our cohort. Although sarcopenia is typically age-related, studies in cirrhotic patients have shown similar results.[26] Tandon et al. reported no effect of age on sarcopenia (OR = 0.99, 95% CI: 0.95–1.03, p = 0.50), and another study by Tandon et al. (n = 159, 60% CTP A) also found no association.[27,28] Fozouni et al. reported similar findings.[29] This suggests that sarcopenia in liver cirrhosis may be primarily driven by disease-specific mechanisms rather than chronological aging.

Our findings support the potential of myostatin as a therapeutic target in cirrhosis-related sarcopenia. Myostatin inhibitors, mostly antibody-based, have undergone clinical testing. MYO-029, a monoclonal antibody developed by Wyeth Pharmaceuticals in 2004, blocks myostatin from engaging its cellular receptors (ActRIIA/B). While Phase 1 and 2 trials were completed, no significant improvements in muscle size, strength, or function were observed, and development was discontinued.[30] Landogrozumab, developed by Eli Lilly, showed modest gains in appendicular lean body mass (+0.44 kg) in Phase 2 trials for age-related sarcopenia and muscle wasting.[31] These therapeutic strategies highlight the promise of targeting myostatin in sarcopenia management.

Limitations

This study has several limitations. First, nutritional status was assessed using the Subjective Global Assessment (SGA) questionnaire, which may be prone to information bias. Second, the study did not consider the effects of medications (e.g., antivirals, diuretics), which could act as unmeasured confounders. Third, the odds ratios in the multivariate analysis were wide, possibly due to small event counts relative to covariates, limiting precision. Post-hoc power analysis was not conducted; interpretation focuses on effect sizes and confidence intervals.[32]

A key methodological limitation is the use of Bioelectrical Impedance Analysis (BIA) to measure muscle mass in cirrhotic patients. BIA is affected by fluid retention, particularly ascites, as it assumes constant conductivity of the body, which is violated in patients with excess fluid. Consequently, BIA may systematically overestimate muscle mass in these patients.[33,34]

CONCLUSION

High myostatin levels are significantly associated with sarcopenia in patients with liver cirrhosis. Additionally, higher degrees of liver damage, as indicated by CTP scores, are associated with elevated myostatin levels. These findings suggest that myostatin may serve as a potential therapeutic target for the management of sarcopenia in cirrhotic patients.

Recommendations

Further research using prospective cohort designs is recommended to establish a causal relationship between myostatin levels and sarcopenia. Future studies should account for the potential confounding effects of medications, such as antiviral therapy and diuretics, on sarcopenia and myostatin levels. Investigations into myostatin-targeted therapies, including antibodies or other inhibitors, are encouraged to explore their efficacy in preventing or treating sarcopenia in liver cirrhosis.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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