# Sarcopenia are Associated with Poor Performance Status in Indonesian Patients with Hepatocellular Carcinoma

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**ABSTRACT**

***Background:*** *Sarcopenia affects hepatocellular carcinoma (HCC) prognosis. Sarcopenia can be assessed by using skeletal muscle index (SMI), measured on transverse CT images at the third lumbar vertebra (L3). HCC staging consists of liver function assessment and Eastern Cooperative Oncology Group performance status (ECOG-PS). ECOG-PS can reflect physical function. This study was aimed to describe the proportion of sarcopenia among adults, using Japan Society of Hepatology criteria and explore association between sarcopenia and poor performance status.*

***Method:*** *The study was conducted in a tertiary hospital during January – October 2021. SMI were evaluated using computed tomography images of L3 in 85 HCC patients. Clinical, laboratory and body composition data were analyzed using bivariate analysis. Logistic regression was performed to obtain an independent association between ECOG-PS and sarcopenic status of HCC patients.*

***Results:*** *Eighty-five HCC patients (median age, 52 years) were analyzed. Sarcopenia was observed in 49,4% of HCC patients. On multivariate binary regression analysis, a poor ECOG-PS remained independently associated with sarcopenia in HCC (adjusted OR = 4.169 (CI 95% = 1.504-11,555), p < 0,006).*

***Conclusion:*** *Sarcopenia has high proportion in HCC patients. There were strong association between ECOG-PS and sarcopenia in HCC.*

***Keywords:*** *sarcopenia, hepatocellular carcinoma, L3-SMI, ECOG, Indonesia*

## ABSTRAK

***Latar Belakang:*** *Sarkopenia mempengaruhi prognosis karsinoma sel hati (KSH). Sarkopenia dapat dinilai dengan mengggunakan indeks massa otot skeletal (IMOS), yang diukur pada potongan melintang gambaran CT setinggi vertebra lumbal 3 (L3). Dalam penilaian klasifikasi KSH terkandung penilaian fungsi hati dan status performa Eastern Cooperative Oncology Group (ECOG). Status performa ECOG merupakan penilaian aktivitas fisik. Studi ini bertujuan untuk menggambarkan proporsi sarkopenia pada dewasa, dengan menggunakan kriteria Japan Society of Hepatology dan menilai hubungan antara sarkopenia dan status performa yang buruk.*

***Metode: S****tudi ini dilakukan di RS tersier selama bulan Januari – Oktober 2021. IMOS dievaluasi dengan menggunakan gambaran CT setinggi L3 pada 85 pasien KSH. Data klinis, laboratorium dan komposisi tubuh dianalisis dengan menggunakan analisis bivariat. Regresi logistic dilakukan untuk memperoleh hubungan independent antara status performa ECOG dan status sarkopenia pada pasien KSH.*

***Hasil:*** *Delapan puluh lima pasien KSH (usia median, 52 tahun) dilakukan analisis. Sarkopenia diamati pada 49,4% pasien KSH. Dengan analisis regresi multivariat, status performa ECOG buruk berhubungan secara independent dengan sarkopenia pada KSH (adjusted OR = 4.169 (95% CI: 1,504-11,555), p < 0,006).*

***Simpulan:*** *Proporsi sarkopenia dijumpai tinggi pada pasien KSH. Terdapat hubungan yang kuat antara status performa ECOG dan sarkopenia pada KSH.*


***Kata kunci:*** *sarkopenia, karsinoma sel hati, IMOS-L3, ECOG, Indonesia*

## INTRODUCTION

Hepatocellular carcinoma (HCC) is a common type of primary liver cancer (90%) with approximately 906,000 new cases and 830,000 deaths.[1] In Indonesia, as any other Asian countries, the main risk factors for HCC are chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV).[1] This disease is related to high mortality, morbidity, and significant health cost.[1-3] Beside clinical problem due to hepatocellular failure and portal hypertension, sarcopenia is another important health problem that is commonly found in HCC. Previously known as an age-associated muscle disease characterized by the progressive loss of muscle mass, this condition also known happened to chronic diseases. In Asian countries, guideline regarding sarcopenia is still limited and only a small number of countries has established definite cut-off for assessment of sarcopenia. Japan Society of Hepatology (JSH) defines sarcopenia as a decrement of skeletal muscle mass shown by low lumbar 3 skeletal muscle index (L3SMI).[4] Sarcopenia is associated with poor outcomes in HCC. In Indonesia, only one study has reported sarcopenia prevalence using a retrospective data.[5]

Sarcopenia evaluation in HCC consists of muscle mass measurement. Muscle mass can be quantified by several modalities such as computed tomography (CT) scan, magnetic resonance imaging (MRI), dual x-ray absorptiometry (DXA), and bioelectrical impedance analysis (BIA). Cross-sectional imaging such as CT has allowed the direct assessment of skeletal muscle mass. Muscle mass evaluation reference standard according to JSH is CT-scan to measure L3SMI.[4,6]

Currently, when determining therapy for HCC, clinicians are still depending on Eastern Cooperative Oncology Group performance status (ECOG-PS) assessment. Evidence suggests that PS assessment can help determine survival.[7] Furthermore, PS assessment is subjective and has inter-observer variability. Physical inactivity as one of the parameters in ECOG-PS has always been known to reduce muscle mass. In addition, Cortellini et al also reported an association between poor ECOG-PS and sarcopenia in patients diagnosed with cancer.[8] Studies suggest earlier detection of low muscle mass or sarcopenia and the factors associated with this condition may aid in improve its treatment and therefore increase prognosis in HCC. The aims of the present study are (1) to estimate sarcopenia prevalence using JSH guideline, and (2) identify association of ECOG-PS with sarcopenia.

## METHOD

This cross-sectional study was approved by the Ethical Committee of Faculty of Medicine Universitas Indonesia/Cipto Mangunkusumo Hospital (No. KET-1509/UN2.F1/ETIK/PPM.00.02/2020) and was conducted in January-October 2021 at the Hepatology Clinic and medical ward of Cipto Mangunkusumo Hospital, Jakarta, Indonesia. We recruited patients aged 18 until 60 years who underwent multiphase abdominal CT-scan with contrast and had the ability to

comply with study procedures including thigh muscle thickness examination (done on the day consent was given) consecutively. Those who had active non-HCC malignancies, HIV infection, and chronic obstructive pulmonary disease were excluded.

Patients' characteristics included in this study were age, sex, etiology of HCC, Child-Pugh score, Barcelona Clinic Liver Cancer (BCLC) stage, Model for End-Stage Liver Disease (MELD) score, MELD-sodium (MELD-Na) score, albumin, and ECOG-PS. The nutritional status examination consisted of body weight, body status, and body mass index. Patients were categorized according to their body mass index (BMI) into < 18,5 kg/m$^2$ and ≥ 18,5 kg/m$^2$, Child-Pugh score into < 8 and ≥ 8, albumin into < 3 g/dL and ≥ 3 g/dL, MELD-Na score into < 15 and ≥ 15, and ECOG-PS into good ECOG-PS (0 and 1) and poor ECOG-PS (2+).

CT scans were performed as standard procedures in HCC diagnosis. The area of total skeletal muscle was segmented at the center plane of the third lumbar vertebra on axial CT scans.[4] Total skeletal muscle areas were assessed using 3D slicer, a software platform for medical segmentation.[9] Several muscle groups were measured: rectus abdominis, transversus abdominis, external and internal obliques, quadratus lumborum, psoas major, and erector spinae. All muscles were added and measured with cutoff values of -29 to 150 Hounsfield Units (HUs). The L3SMI was calculated as follows: L3SMI (cm$^2$/m$^2$) = skeletal muscle area at L3 (cm$^2$) divided by square of body height (m$^2$). A representative case is presented in Figure 1.

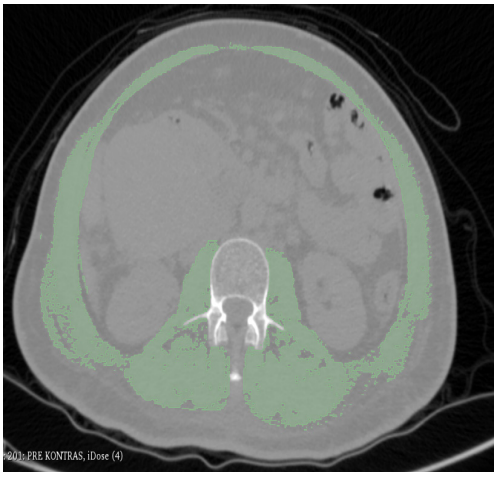


**Figure 1. CT scan of a representative case. Cross-sectional areas (cm2) of skeletal muscles at the third lumbar level were measured by manual tracing on the CT images, and their sum was calculated. The green area is showing skeletal muscle at the third lumbar level. CT, computed tomography.**

JSH criteria for sarcopenia cut-off is less than 38 cm$^2$/m$^2$ for females and 42 cm$^2$/m$^2$ for males. Definition of sarcopenia is low muscle mass. Data from additional laboratory and radiology (CT scan) examinations were obtained by the main researcher and research assistants. Subjects would undergo body weight and height measurements.

Statistical analyses were performed using SPSS version 23.0. The statistical power was set at 80%, whereas 5% for the α value. The minimum sample size was 74 subjects. Baseline and clinical characteristics of research subjects were presented in tabular form. Categorical data were presented in numbers and percentages. Numerical data were presented in mean and standard deviations if the data distribution was normal, and median and minimum and maximum values if the data distribution was not normal.

To determine whether ECOG-PS is associated with sarcopenia in HCC patients, a bivariate analysis was first performed on variables associated with sarcopenia. The bivariate analysis of each variable was carried out using Chi-square test or Fisher-Exact test as the alternative if the conditions for Chi-square test were not met. The odds ratio (OR) values of each variable associated with sarcopenia were obtained. Significant variables with a p-value < 0.25 in bivariate analysis would be included in the logistic regression analysis. Logistic regression analysis was executed to find the relationship between ECOG-PS and sarcopenia in HCC patients after being adjusted for other significant variables.

## RESULTS

There were 95 subjects who met the inclusion criteria and 10 subjects who did not, so that a total of 85 subjects were analyzed. The complete characteristics of the research subjects are shown in Table 1.

**Table 1. Research subjects characteristics**

| Variables | n = 85 |
|---|---|
| Age in years, median (min-max) | 52 (35-60) |
| BMI in kg/ m$^2$, median (min-max) | 22,68 (15,63-37,95) |
| Gender, n (%) | |
| Male | 63 (74,1) |
| Female | 22 (25,9) |
| Sarcopenia, n (%) | |
| Yes | 42 (49,4) |
| No | 43 (50,6) |
| Child-Pugh class, n (%) | |
| Class A | 46 (54,1) |
| Class B | 31 (36,5) |
| Class C | 8 (9,4) |

**Table 1. Research subjects characteristics (advanced)**

| Variables | n = 85 |
|---|---|
| HCC etiology, n (%) | |
| Hepatitis B | 51 (60) |
| Hepatitis C | 20 (23,5) |
| Hepatitis Non-B Non-C | 13 (15,3) |
| Hepatitis B and C | 1 (1,2) |
| BCLC criteria, n (%) | |
| Stadium 0 | 1 (1,2) |
| Stadium A | 18 (21,2) |
| Stadium B | 29 (34,1) |
| Stadium C | 30 (35,3) |
| Stadium D | 7 (8,2) |
| ECOG performance status, n (%) | |
| ECOG 0-1 | 56 (65,9) |
| ECOG 2+ | 29 (34,1) |
| Albumin in g/ dL, mean (SD) | 3,42 (0,67) |
| Bilirubin in mg/ dL, median (min-max) | 1,03 (0,28-36,85) |
| INR, median (min-max) | 1,11 (0,85-2,78) |
| Creatinine in mg/ dL, median (min-max) | 0,8 (0,4-2,6) |
| Sodium in mEq/ L, median (min-max) | 135 (120-143) |
| MELD score, median (min-max) | 9 (6-32) |
| MELD-Na score, median (min-max) | 13 (6-33) |
| L3 skeletal muscle index in $cm^2$/ $m^2$, mean (SD) | 41,13 (9,31) |

Note: min-max: minimal – maximal, n: number, BMI: body mass index, SD: standard deviation, kg: kilograms, mm: millimeter, cm: centimeter, m: meter

Bivariate analyses were performed to determine the association between sarcopenia and body mass index, gender, Child-Pugh score, ECOG-PS, albumin level, and MELD-Na score (Table 2 and 3). From various baseline characteristics shown in the table, statistically significant associations are found between sarcopenia in HCC patients and ECOG-PS of 2+ (p = 0,003) and MELD-Na score ≥ 15 (p = 0,023). BMI, gender, Child-Pugh score, and albumin was not associated with sarcopenia in HCC.

Out of Table 3, variables known to have p value < 0,25 were MELD-Na and BMI. Two variables were entered one by one to the logistic regression analysis and analyzed based on hierarchically well formulated (HWF) principle.

Multivariate analysis showed a statistically significant association between high ECOG-PS (2+) and sarcopenia with adjusted odds ratio (aOR) = 4.169 (95% CI = 1.504-11,555).

## DISCUSSION

In our study, the median age of patients with HCC was 52 years. This result is similar to the study conducted by Hasan et al (2016) and Jasirwan et al (2020), which reported that the median age of patients with HCC was 54 years and 55 years consecutively.[10,11] In Asian countries, such as Indonesia, which have a high prevalence of HBV infection, HCC usually occurs under 60 years old.[12] This study found the male to female

**Table 2. Association between ECOG performance status and sarcopenic HCC patient**

| Variable | Sarcopenia | Non-Sarcopenia | p value | Odds ratio (95% CI) |
|---|---|---|---|---|
| ECOG Performance Status, n (%) | | | | |
| ECOG 2+ | 21 (72,41) | 8 (27,59) | **0,003** | **4,375 (1,646-11,630)** |
| ECOG 0-1 | 21 (37,5) | 35 (83,93) | | |

**Table 3. Association between confounding and sarcopenic HCC patient**

| Variable | Sarcopenia | Non-Sarcopenia | P value | Odds Ratio (95% CI) |
|---|---|---|---|---|
| BMI, n (%) | | | | |
| < 18,5 kg/ $m^2$ | 6 (75) | 2 (25) | 0,147 | 3,417 (0,649-18,001) |
| ≥ 18,5 kg/ $m^2$ | 36 (46,75) | 41 (53,25) | | |
| Gender, n (%) | | | | |
| Male | 29 (46,03) | 34 (53,97) | 0,294 | 0,590 (0,221-1,579) |
| Female | 13 (59,10) | 9 (40,90) | | |
| Child-Pugh score, n (%) | | | | |
| ≥ 8 | 11 (52,38) | 10 (47,62) | 0,754 | 1,171 (0,437-3,141) |
| < 8 | 31 (43,48) | 33 (56,52) | | |
| Albumin, n (%) | | | | |
| < 3 g/ dL | 15 (55,56) | 12 (44,44) | 0,440 | 1,435 (0,573-3,593) |
| ≥ 3 g/ dL | 27 (46,55) | 31 (53,45) | | |
| MELD-Na, n (%) | | | | |
| ≥ 15 | 22 (64,71) | 12 (35,29) | **0,023** | **2,842 (1,155-6,992)** |
| < 15 | 20 (39,22) | 31 (60,78) | | |

**Table 4. Multivariate logistic regression analysis sarcopenia in HCC**

| Variables | OR (95% CI) | Delta OR |
|---|---|---|
| *Crude* : ECOG performance status 2+ | 4,375 (1,646-11,630) | |
| *Adjusted :* | | |
| (+) MELD-Na ≥ 15 | 3,807 (1,400-10,353) | 14,92% |
| (+) BMI < 18,5 kg/ $m^2$ | 4,169 (1,504-11,555) | 8,68% |

ratio was 3 to 1. This characteristic is similar to other studies. A study by Salman et al in Egypt showed that 72% of subjects with HCC included were men and the remaining 28% women, with the mean age of the subjects was around 53.4 years old.[13] More men are found to be associated with HCC compared to women. This phenomenon is caused by the presence of androgen receptors in men that contributes to the progression of HCC. These androgen receptors inhibit the role of p-53 and DNA repair and produce oxidative stress.[14]

In this study, 49,4% of the subjects were diagnosed with sarcopenia. Various research stated that sarcopenia is found in 30-70% of patients with liver cirrhosis. This is due to malnutrition, impaired protein and myostatin synthesis.[15] Most subjects in this study had ECOG-PS 2+ (35%). A study by Yang et al, in Africa showed that in African countries other than Egypt, the number of subjects with ECOG-PS 0 and 1 was 42% and ECOG-PS 2+ was 58%, indicating that patients had already shown poor liver performance status at the initial presentation of the disease.[16] High number of ECOG-PS 2+ in this study shows that HCC with poor performance status is still underdiagnosed, possibly due to the lack of comprehensive surveillance program.

This condition is quite different from the research in Japan done by Nishikawa et al and Hanai et al which observed that sarcopenia was 65,1% and 63% respectively.[15,17] In this research, HCC patients aged 60 years old were excluded which primary sarcopenia usually occurred. In research by Nishikawa et al, the age median was 72 years old. While Hanai et al found that the age median was 65 years old.[17] Other things also showed that in most of subjects in Japan research, HCC patients had undergone a lot of therapy protocols before starting systemic therapy like sorafenib. In this research, most of patients were in naïve conditions which were referred from type B hospitals. Previous HCC therapy can decrease liver function, decrease quality of life and increase sarcopenia incidence in HCC.

The most common etiology of HCC in this study was hepatitis B (60%), followed by HCV infection, non-B, non-C infection, and coinfection of HBV and HCV. Hepatitis B infection plays a role in 50-80% of cases of HCC worldwide with a high prevalence seen in several countries such as Indonesia.[18]

To assess the association between ECOG-PS and sarcopenia in HCC, firstly associations between confounding variables and sarcopenia in HCC need to be assessed. Confounding variables in this research were MELD-Na and BMI.

MELD-Na score, known as the best modality in predicting mortality in liver cirrhosis patients, was also related to sarcopenia in some research. In liver cirrhosis, where there is liver synthesis dysfunction, loss of muscle mass can occur rapidly.[14] Under normal conditions, muscle mass will decrease 1% each year from 30 until 70 years and this thing is going to increase to 1,5% per year after 70 years old. However, Hanai et al found that muscle mass decrement per year in liver cirrhosis patients is 2,2%, which showed that liver cirrhosis complication will accelerate skeletal muscle depletion. Skeletal muscle depletion in liver cirrhosis has been reported to decrease liver function severity judged as Child-Pugh score. Based on the research done by Hanai et al, muscle mass decrement per year was correlated with Child-Pugh and MELD score.[17] Another research by Kim et al showed that there was a negative correlation between MELD-Na score and ratio between psoas muscle thickness, a muscle mass indicator in liver cirrhosis patients with ascites.[19] In this research, MELD-Na score act as a confounding variable to the association between ECOG-PS and sarcopenia. This condition is understandable considering that high MELD-Na score, as a sign of liver function severity, was usually accompanied by a decrement of muscle mass.

This study showed that ECOG-PS was related to sarcopenia in HCC, independent of several body composition factors and prognostic factors such as BMI, albumin, MELD-Na score, and Child-Pugh. Multivariate analysis identified ECOG-PS was associated with sarcopenia in HCC. This research was consistent with the previous one.[20]

Decrease of muscle mass and strength often occur in chronic diseases. Therefore, it is not unusual to see a significant difference between ECOG-PS 2+ and sarcopenia. Performance status is a modality to measure the physical status and activity of daily living, which is related to muscle mass and strength. A study by Ha et al (2018) found sarcopenia in 34.4% of subjects with ECOG-PS 0-1 and 38.1% of subjects with ECOG-PS 2+.[21] Another study by Nishikawa et al (2017) found sarcopenia in 64.8% of subjects with ECOG-PS 0-1 and 80% of subjects with ECOG-PS 2+.[19] Antonelli et al (2018) found sarcopenia in 51.4% of subjects with ECOG-PS 0-1 and 71.4% of subjects with ECOG-PS 2+. An increase in the prevalence of sarcopenia in subjects with ECOG-PS 2+ indicates a condition called “cancer cachexia,” a state of loss of muscle mass and body fat in patients with more advanced stages of cancer.[22] A systematic review

about the association between sarcopenia and physical activity in the elderly showed that physical activities reduced the incidence of sarcopenia with OR = 0.45. Physical activities will increase muscle strength and muscle mass in adulthood. Resistance training is specifically the best way to prevent sarcopenia.[23]

A study conducted by Ohashi et al (2018) also showed that sarcopenia was more commonly found in patients with sedentary lifestyle with less physical activities. A study in cases of chronic liver disease by Ohashi et al, also showed that a decrease in skeletal muscle mass could occur in early stages of the disease due to impaired protein synthesis. Physical exercises and nutritional therapy would improve physical function and increase muscle mass in patients with chronic liver disease.[24]

After adjustment for other variables, ECOG-PS was the parameter with the strongest association to the incidence of sarcopenia in HCC (aOR) = 4.169 (95% CI: 1.504-11.555). Daily physical activities are disrupted in patients with ECOG-PS 2+, which will affect the incidence of sarcopenia.[24]

This is the first research in Indonesia that prospectively examines sarcopenia in HCC patients. This study also uses primary data therefore it does not experience recording bias. This study defines sarcopenia by using measurements of muscle mass according to the gold standard in chronic liver disease. Patients over 60 years old were excluded to show the true disease entity, not as part of aging. The limitation of this study is that it cannot be applied to HCC patients aged 60 years old and over. Another limitation is the small sample size of women in this study.

In summary, measurement of patient performance and muscle mass, using validated and easily replicated tools, may aid clinician to improve HCC patients. These assessments would enable more accurate prediction of successful therapeutic goals for patients at potential risk from planned treatments and thereby allowing intervention to be targeted for each HCC patients.

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