

Sarcopenia as an indicator of nutritional status and outcome predictor for colorectal cancer in Javanese ethnic



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ABSTRACT

Background: Sarcopenia is a negative predictor of colorectal cancer outcomes, while colorectal cancer is at risk of developing malnutrition due to the disease process. This study aims to determine the relationship between sarcopenia and nutritional status and analyze the effect of sarcopenia on the outcome of rectal cancer patients.

Method: A cross-sectional study was conducted on colorectal cancer patients of Javanese ethnicity who performed preoperative abdominal CT scans at dr. Sardjito Hospital in Yogyakarta between June and December 2019. Sarcopenia is based on measuring muscle mass index at the third lumbar vertebra level $<36.0 \text{ cm}^2/\text{m}^2$ for men and $<29.0 \text{ cm}^2/\text{m}^2$ for women. Statistical analyzes using SPSS version 20 for Windows were performed to find out the correlation.

Results: Of 46 patients, 56.5% were male and 43.5% female, with a mean age of 53.57. Sarcopenia was found in 47.8% of patients, mostly in women than men (63.6% vs. 36.4% $p=0.019$). Underweight was mostly found in the sarcopenia group compared to non-sarcopenia (59.1% vs. 20.8% $p=0.019$). The sarcopenia group has longer LOS than non-sarcopenia (14.73 ± 13.474 vs. 12.29 ± 4.165 ; $p=0.404$). The mortality of the sarcopenia group was 1.56 times higher compared to the non-sarcopenia (57.1% vs. 42.9%; $OR=1.56$; $95\%CI=0.307-7.890$; $p=0.964$). Haemoglobin, albumin, total protein, CEA, histopathology, tumor location and procedure were not significantly correlated to sarcopenia.

Conclusion: Underweight nutritional status and females are correlated with sarcopenia. Sarcopenia tends to be treated longer and has higher mortality than non-sarcopenia.

Keywords: Sarcopenia, Nutritional Status, Rectal Cancer, Outcome.

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INTRODUCTION

Colorectal cancer is still a health problem and includes three cancers with the highest prevalence in Indonesia.¹ The incidence rate of colorectal cancer per 100,000 population in Indonesia is 19.1 for men and 15.6 for women. The incidence of colorectal cancer is higher in men (54%) than in women (46%). Peak cancer cases occur at the age of 50-54 years. DKI Jakarta, Central Java, and DIY Yogyakarta are the three provinces with the highest incidence of colorectal cancer.^{2,3}

The therapeutic response to colorectal cancer is determined by prognostic and predictive factors, which generally consist of clinical parameters, tumor markers, and genetic and epigenetic changes. Several studies report that the composition and distribution of skeletal muscle mass show prognostic implications in patients with colorectal cancer. Sarcopenia, a state of

decreased skeletal muscle mass, is known to be associated with negative outcomes.⁴⁻⁷

Patients with malignancy are at risk of developing malnutrition. Malnutrition is characterized by weight loss, the cardinal sign of cachexia cancer. Cachexia cancer contributes to a poor prognosis through progressive energy depletion and body protein reserves. Therefore, it is important to determine the presence of cachexia through routine preoperative examination. Decreased skeletal muscle mass, weight loss, and decreased BMI are part of cachexia syndrome. Recognizing early sarcopenia is a valuable step in establishing a diagnosis of malnutrition that will continue as cachexia syndrome.⁸⁻¹⁰ This study aims to determine the correlation between sarcopenia and nutritional status. Furthermore, it will also be analyzed how the effect of sarcopenia on mortality and length of stay as outcome rectal cancer patients in special local Javanese ethnic

group di Yogyakarta.

METHODS

Data sources and research population

This study was registered by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Gadjah Mada University, Yogyakarta (Ref.No:KE/FK/1028/EC/201). This research is a cross-sectional study carried out at the Central General Hospital, dr. Sardjito Yogyakarta. Data from all rectal cancer patients of the Javanese ethnic group based on classification ethnic group on medical records and taken by consecutive sampling technique, treated in the surgical ward were included in this study from June to December 2019. Inclusion criteria were every adult patient of the Javanese ethnic group undergoing curative resection or palliative therapy where the pathology had

confirmed a rectal adenocarcinoma that had undergone a preoperative abdominal CT scan. Patients were excluded if they underwent emergency surgery, patients who did not have a preoperative CT scan and non-Javanese ethnic. Demographic, anthropometric and clinical data, including weight and height, body mass index (BMI), nutritional status, serum albumin levels, total protein levels, CEA and hemoglobin levels, history of previous operations, TNM stage, operating goals and therapeutic procedures, length of stay in the hospital, and in-hospital mortality were analyzed.

Sarcopenia measurement: CT scan analysis

The total cross-sectional area of muscles as high as the third lumbar vertebra (L3) inferiorly is measured using manual techniques to measure sarcopenia. Muscles in the L3 region containing psoas, spinal erector, quadratus lumborum, transversus abdominis, external and internal obliques and rectus abdominis are visualized. All these muscles are identified through the HU threshold (Hounsfield unit) range of 29 to 150. A manual outline on CT images measures the cross-sectional area (cm²) of skeletal muscle in the L3 region. The muscle area is normalized to height (m²) and reported as an L3 muscle index (cm²/m²). The cut-off value used for the diagnosis of sarcopenia is the same as that used by Huang DD et al., 36.0 cm²/m² for men and 29.0 cm²/m² for women. All patients with a muscle mass index below this threshold were classified as sarcopenic according to sex.⁵ For this study, sarcopenia was defined as an absolute variable of the patient or non-sarcopenic.

Statistical analysis

Relevant variables are transcribed to SPSS version 20 for Windows to enable statistical analysis. The univariate analysis describes the patient population in which continuous variables are summarized in averages, and categorical variables are presented as tabulations in percentages. Bivariate analysis using the Chi-square test was used to analyze categorical variables by categories. With the square test, the predictive factors for mortality and length of stay can be determined by displaying

the odds ratio in the exposed group. The level of significance is set at 5%.

RESULTS

We included 46 colorectal cancer patients with an age average of 53.57±11.77 years old; men were 56.5%, and females were 43.5%. Normal nutritional status was 60.9% and under nutritional status was 39.1%. Most subjects had no history of previous operations (63.0%). Serum albumin levels were mostly <3.5 mg/dL (60.9%), and total protein was mostly > 6 mg/dL (78.3%). Blood hemoglobin levels were mostly <12 mg/dl (69.6%). CEA levels were mostly >5ng/dL (65.2%). Adenocarcinoma moderate differentiation is the highest histopathological type (43.5%). The majority of tumor location was at the distal third of the tectum (60.9%) and had advanced stages (stages 3 and 4) (87%). The treatment goals were mostly palliative therapy (63%), while curative resection was 37.0%. The colostomy procedure was 43.5%, chemotherapy 19.6%, Miles 19.6%, LAR 13%, and Hartmann 4.3%. The average length of stay was 13.46±9.75 days. 15.2% of patients died. Among 46 patients, 22 (47.8%) had sarcopenia, as shown in Table 1.

The differences in characteristics of the sarcopenic and non-sarcopenic groups are compared in Table 2. Of 22 sarcopenic patients, 36.4% were males, and 63.6% were females. Sarcopenia is more common in women than men (p = 0.019). Underweight nutritional status is more common in sarcopenia than normal (p = 0.019). Serum albumin levels, total protein levels, blood hemoglobin levels, CEA levels, history of previous operations, type of histopathology, tumor location, clinical stage and therapeutic goals (curative or palliative) were not statistically significant (p>0.05). The colostomy procedure is the most common in both sarcopenia and non-sarcopenia groups. In the sarcopenia group, most colostomy procedures are performed. LAR and Miles procedures are mostly in the non-sarcopenia group. Chemotherapy and Hartmann procedure were performed more in the sarcopenic group. There was no statistical difference (p> 0.05). There was no statistical difference in average age in the sarcopenic

and non-sarcopenic groups. Length of stay (LOS) statistically, there was no significant difference even though in the sarcopenia group LOS obtained relatively longer than non-sarcopenia group (14.73±13.474 vs. 12.29±4.165; p=0.404).

Mortality was 57.1% in the sarcopenia and 42.9% in the non-sarcopenia group. The sarcopenia group had mortality rates 1.56 times higher than non-sarcopenia (OR 1.56; 95%CI=0.307-7.890). There were no statistical differences between the two groups (p = 0.964), as seen in Table 3.

DISCUSSION

In this study, we performed skeletal muscle counts with preoperative abdominal CT imaging analyses routinely performed in cancer patients treated for curative resection purposes and palliative therapy. CT is widely used to measure muscle mass, with errors ranging from 1 to 4%; thus, it is considered a gold standard. Using this approach, we found the prevalence of sarcopenia was 47%. The prevalence of sarcopenia that we obtained is in accordance with a meta-analysis study involving 70 studies with 21,875 patients where the incidence of sarcopenia ranged from 2.1 to 83.3% and as many as 88.4% of studies used skeletal muscle index at the level third lumbar on CT to determine sarcopenia.^{12,13} The incidence of sarcopenia depends mostly on how define the diagnostic cut-off point for sarcopenia. Skeletal muscle index is a criterion that is often used. Although some Asian criteria were proposed the validation among countries still needs to be investigated for efficacy and accuracy, including in Indonesia, because of the difference in body shape and diet habits.^{14,15} Our study uses the sarcopenia cut-off for colorectal cancer based on the research of Huang DD et al. because it is quite relevant to the subject of this study, rectal cancer.⁵ Whether this cut-off matches the profile of the Javanese population still needs further investigation.

We found that the prevalence of sarcopenia was higher in women than in men (63.6% vs. 36.4%). The currently available literature is unclear regarding sex differences in the prevalence of sarcopenia. Some reported that sarcopenia was more likely male, while others reported a higher

Table 1. Demographic, clinical, and histopathological characteristics of rectal cancer patient.

Variabel	Value
Sex	
Male	26 (56.5)
Female	20 (43.5)
Nutritional status / BMI	
Underweight	18 (39.1)
Normal	28 (60.9)
Albumin serum (g/dL)	
< 3.5	28 (60.9)
> 3.5	18 (39.1)
Protein total (g/dL)	
< 6	10 (21.7)
> 6	26 (78.3)
Hemoglobin (g/dL)	
< 12	32 (69.6)
> 12	14 (30.4)
CEA (ng/dL)	
> 5	30 (65.2)
< 5	16 (34.8)
Previous operation	
Yes	17 (37.0)
No	29 (63.0)
Histopathology type	
Adenocarcinoma poorly differentiated	10 (21.7)
Adenocarcinoma moderately differentiated	20 (43.5)
Adenocarcinoma well differentiated	14 (30.4)
Others	2 (4.3)
Tumor Location	
Proximal	11 (23.9)
Medial	7 (15.2)
Distal	28 (60.9)
Stadium (TMN)	
Late (Stadium 3 and 4)	40 (87.0)
Early (Stadium 1 and 2)	6 (13.0)
Treatment Purpose	
Curative Resection	17 (37.0)
Palliative Treatment	29 (63.0)
Treatment procedure	
Colostomy	20 (43.5)
Hartmann	2 (4.3)
Chemotherapy	9 (19.6)
Low Anterior Resection	6 (13.0)
Miles Procedure	9 (19.6)
Mortality	
Dead	7 (15.2)
Survive	39 (84.8)
Sarcopenia	
Yes	22 (47.8)
No	24 (52.2)
Age (years)	53.57±11.77
Length of Stay (days)	13.46±9.75

Values are presented as mean ± standard deviation or number (%).

risk of sarcopenia in females, especially among community-dwelling elderly adults. These inconsistent results may be due to differences in racial characteristics, cultural backgrounds, dietary patterns, and physical activity among the different studies.¹⁶ We Need further research to see this correlation concerning rectal cancer. The mean age of rectal cancer patients in this study was 53.57±11.77 years. It correspond^{ed} to the peak of rectal cancer cases in Indonesia (50-54 years).² However, there was no age difference in the sarcopenia and non-sarcopenia groups. In general, sarcopenia is a geriatric syndrome that occurs in old age. In cases of malignancy, especially in rectal cancer, sarcopenia can occur earlier because of the disease process and treatment procedures. In this situation, sarcopenia can occur earlier and is not a geriatric syndrome.¹⁷

Underweight nutritional status (BMI <18 kg/m²) was significantly higher in the sarcopenic group, which statistically shows a significant association compared to the non-sarcopenic group. This finding is consistent with the literature that sarcopenia increases at lower BMI. This reduction in muscle mass can be associated with malnutrition due to cachexia cancer regardless of the stage (from curative to palliative).^{17,18}

Most sarcopenia (95%) patients were in an advanced stage, higher than the non-sarcopenia group (79.2%). This proportion causes no difference in the influence of the cancer stage on the prevalence of sarcopenia. But clinically, it was found that most sarcopenia patients are in the advanced stage. This is consistent with the clinical course of malignancy, where the risk of cancer cachexia is increasing.¹⁹ Other laboratory indicators that can be used to assess nutritional statuses, such as total protein levels, serum albumin, and blood hemoglobin in this study, did not show a significant relationship to sarcopenia.

The correlation between sarcopenia and CEA level, previous surgery, histopathology type, tumor location, goals of therapy (curative and palliative therapy) and treatment procedure were not statistically related. This finding is the same as several studies analyzing sarcopenia's relationship to colorectal

Table 2. Demographic, clinical, and pathological characteristics of patients with sarcopenic compared with patients without sarcopenia.

Variable	Sarcopenia		p
	Yes	No	
Sex			
Male	8 (36.4%)	18 (75.0%)	0.019*
Female	14 (63.6%)	6 (25.0%)	
Nutritional status / BMI			
Underweight	13 (59.1%)	5 (20.8%)	0.019*
Normal	9 (40.9%)	19 (79.2%)	
Albumin serum (g/dL)			
< 3.5	14 (63.6%)	14 (58.3%)	0.948
> 3.5	8 (36.4%)	10 (41.7%)	
Protein total (g/dL)			
< 6	6 (27.3%)	4 (16.7%)	0.484
> 6	16 (72.7%)	20 (83.3%)	
Hemoglobin (g/dL)			
< 12	16 (72.7%)	16 (66.7%)	0.900
> 12	6 (27.3%)	8 (33.3%)	
CEA (ng/dL)			
> 5	17 (77.3%)	13 (54.2%)	0.182
< 5	5 (22.7%)	11 (45.8%)	
Previous operation			
Yes	6 (27.3%)	11 (45.8%)	0.319
No	16 (72.7%)	13 (54.2%)	
Histopathology type			
Adenocarcinoma poorly differentiated	5 (22.7%)	5 (20.8%)	0.382
Adenocarcinoma moderately differentiated	10 (45.5%)	10 (41.7%)	
Adenocarcinoma well differentiated	5 (22.7%)	9 (37.5%)	
Others	2 (9.1%)	0 (0%)	
Tumor location			
Proximal	6 (27.3%)	5 (20.8%)	0.524
Medial	2 (9.1%)	5 (20.8%)	
Distal	14 (63.6%)	14 (58.3%)	
Stadium (TMN)			
Late (Stadium 3 and 4)	21 (95.5%)	19 (79.2%)	0.190
Early (Stadium 1 and 2)	1 (4.5%)	5 (20.8%)	
Treatment purpose			
Curative resection	5 (22.7%)	12 (50.0%)	0.108
Palliative treatment	17 (77.3%)	12 (50.0%)	
Treatment procedure			
Colostomy	12 (22,54)	8 (33,33)	0.082
Hartmann procedure	2 (9,00)	0 (0)	
Chemotherapy	5 (22,72)	4 (16,66)	
Low anterior resection	1 (4,54)	5 (20,82)	
Miles procedure	2 (9,00)	7 (29,16)	
Age (years)	53.450±13.479	53.670±10.260	0.953
LOS (days)	14.730±13.474	12.290±4.165	0.404

Values are presented as mean ± standard deviation or number (%); *Statistically significant if p-value less than 0.05

Table 3. Results of analysis of sarcopenia on mortality.

Variable	Mortality		OR (95% CI)	p
	Dead	Survive		
Sarcopenia				
Yes	4 (57.1%)	18 (46.2%)	1.56 (0.307-7.890)	0.964
No	3 (42.9%)	21 (53.8%)	ref	

Values are presented as numbers (%)

cancer.^{18,19,20} Based on our study results, therapeutic procedures in the sarcopenia group were aimed more at palliative therapy (colostomy and chemotherapy), while those in the non-sarcopenia group were more curative. The selection of procedures in these two groups is, in our opinion, in accordance with the prognosis of the two groups, so the outcomes (LOS and mortality) were not significant in the two groups.

In our study, patients with sarcopenia have longer hospitalizations, although statistically, there is no significant difference compared to non-sarcopenia (14.73±13.474 vs. 12.29±4.165 days, $p=0.404$). The relationship between LOS and sarcopenia in malignancy is still controversial. Still, several studies have found a clear relationship where sarcopenia is a predictive factor for high LOS.^{7,18,20} Further prospective studies are needed to confirm and expand the findings.

Sarcopenia has been reported as a risk factor for worse outcomes in some reports, including that sarcopenia is negatively associated with overall survival, an independent risk factor for complications following surgery, the risk for the occurrence of postoperative sepsis and worse colorectal cancer prognosis regardless of stage.^{4,5,6,11} While other studies mentioned that sarcopenia is not a predictive factor for length of stay, hospital stay, or time for mobilization, sarcopenia did not worsen disease-free survival, overall survival and postoperative complications. Readmission was significantly increased in patients with sarcopenia.^{7,12} But in this study, mortality in the sarcopenia and non-sarcopenia groups did not reach a statistically significant difference, although the sarcopenia group died 1.56 times compared to those without sarcopenia (OR 1.56; 95% CI 0.307 - 7.89). The results of this study are different compared to the studies that

have been done.^{13,20,21} We assume this difference because the sarcopenia group is mostly palliative therapy while the non-sarcopenia group is more curative. The decision to do palliative therapy is more suitable to the patient's prognosis, where patients with sarcopenia are more at risk of complications and higher mortality.

In addition to the limited number of samples in each group, the weaknesses of our study were we have not explicitly separated patients who were included in certain categories, such as resectable or non-resectable and metastatic or non-metastatic, which might give different results. For future studies, we suggest defining sarcopenia at different stages of the course of rectal cancer to see the outcome because of sarcopenia at each stage of the disease course. The cut-off value of sarcopenia used adopts the cut-off value of research from China which is likely to be different from the Indonesian population, which currently does not have a standard value for sarcopenia.^{22,23} Nonetheless, this research is the initial sarcopenia study conducted at our institution and carried out on the rectal cancer population of ethnic Javanese, who demographically represent the Indonesian population. We recommend a study to determine the cut-off sarcopenia for the Indonesian population and a study with a larger sample size based on the cancer stage.

CONCLUSION

In conclusion, reduced skeletal muscle mass (sarcopenia) is significantly associated with female and underweight nutrition in rectal cancer patients. The length of stay of the sarcopenia group was longer than the non-sarcopenia group. Mortality was greater in the sarcopenia group, although there was no statistical difference.

CONFLICT OF INTEREST

The authors declare that there is no competing interest regarding the manuscript.

ETHICAL CONSIDERATION

This research was conducted based on the ethical conduct of research from the Ethics Committee of the Medical Faculty, Universitas Gadjah Mada, Dr. Sardjito General Hospital, Yogyakarta, Indonesia with permission number KE/FK/1028/EC/2019.

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AUTHOR CONTRIBUTION

All authors contributed to the study from the conceptual framework, data gathering, and analysis until the study's results were interpreted upon publication. The author thanks dr. Bambang Purwanto Utomo Sp.R and dr. Juanda from the Radiology Department of RSUP dr. Sardjito Yogyakarta for supervision and analysis of abdominal CT scan examination. Also, to Ms. Dewi from Clinical Epidemiology and Biostatistics Unit (CEBU) RSUP dr. Sardjito for statistical data analysis.

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