



Original Article

Association between preoperative sleep disturbance and low muscle mass in patients with gastrointestinal cancer

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Abstract. [Purpose] Low muscle mass and sleep disturbance are common among geriatric patients with cancer. In patients with gastrointestinal cancer, low muscle mass is considered an indicator of poor prognosis. In the recent years, sleep disturbance has attracted much attention as a factor for low muscle mass among community-dwelling elderly individuals; however, such associations are unclear in patients with cancer. The present study investigated the relationship between preoperative sleep disturbance and low muscle mass in patients with gastrointestinal cancer. [Participants and Methods] This cross-sectional survey enrolled 86 elderly patients (aged more than 60 years) with gastrointestinal cancer who were scheduled for curative surgery. Low preoperative muscle mass was defined according to Asian Working Group for Sarcopenia criteria. Sleep disturbance was assessed using the Japanese version of the Pittsburgh Sleep Quality Index, including the subscales. [Results] Twenty-seven patients (31%) were classified as having low muscle mass. After adjusting for confounding factors, bad sleep quality, determined by the subscales, was significantly associated with low muscle mass. [Conclusion] Our results suggest that the evaluation of sleep quality is imperative for addressing low preoperative muscle mass in patients with gastrointestinal cancer.

Key words: Low muscle mass, Sleep disturbance, Gastrointestinal cancer

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INTRODUCTION

Low muscle mass is more common among preoperative geriatric patients with cancer than among healthy older people, having a prevalence of 41.5% among preoperative patients with gastric cancer versus 26.8% and 22.8% among healthy men and women, respectively^{1, 2)}. Factors affecting low muscle mass among patients with cancer are intricate. Alterations in hormonal mediators, as well as the release of tumor factors and cytokines, can all lead to low muscle mass³⁾. Considering that low muscle mass predicts postoperative complications and is associated with decreased recurrence-free survival and decreased survival rates in gastrointestinal cancer^{1, 4, 5)}, low preoperative muscle mass remains a major problem that must be addressed.

In recent years, sleep disturbance has attracted much attention as a factor for low muscle mass among community-dwelling elderly individuals. Sleep disturbance affects hormonal mediators and cytokines, which can lead to low muscle mass^{6, 7)}. For

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example, lack of sleep time associated with increased cortisol, which is a catabolism hormone⁸). Previous studies have shown that bad sleep quality, efficiency and prolonged time to fall asleep are associated with low muscle mass among community dwelling elderly^{9, 10}). Given that certain types of sleep disturbances are involved in the development of low muscle mass, the assessment of various types of sleep disturbances is imperative.

Sleep disturbance has been overlooked by the oncology community¹¹). Nonetheless, considering that sleep disturbance is also a common symptom among patients with cancer¹²), such a problem needs considerable attention. It is necessary to examine the relationship between sleep disturbance and low muscle mass, which affects prognosis. However, such associations have been unclear in patients with cancer. If the relationship between preoperative sleep disturbance and low muscle mass can be clarified, the assessment of sleep might be useful for addressing low muscle mass when we provide rehabilitation. The present study, therefore, investigated the association between preoperative sleep disturbance and low muscle mass, while evaluating certain types of sleep disturbance.

PARTICIPANTS AND METHODS

This cross-sectional study was conducted between July 2016 and April 2017 at a single university hospital located in an urban area. A total of 161 patients with gastrointestinal cancer aged 60 years and older and who scheduled for curative surgery were enrolled. The exclusion criteria included the presence of simultaneous cancers, declining of consent, or any missing values. Among the 161 patients recruited, 139 (86%) agreed to participate in the current study. A total of 53 patients were excluded because of simultaneous cancers (n=1) or at least one missing values (n=52). Ultimately, 86 patients were enrolled in the present study (male: 72, female: 14, age: 70.5 ± 7.08 years, mean ± SD). After obtaining a written consent, all included patients completed measurements before surgery. Ethical approval for the present study was provided by the Ethics Committee of the Kobe University Graduate School of Health Sciences (approval number 440). All participants were properly informed about the study and signed written consent forms prior to participation in accordance with the Declaration of Helsinki.

Weight, muscle mass, and body mass index (BMI) were assessed using multi-frequency bioelectrical impedance with eight electrodes (Inbody430; Inbody Japan, Tokyo, Japan). Low muscle mass was defined as a skeletal muscle mass index (SMI) of <7.0 and <5.7 kg/m² for men and women, respectively, according to the criteria of the Asian Working Group for Sarcopenia¹³). Patients were divided into “low muscle mass” and “no low muscle mass” groups, whereas SMI and BMI were calculated using the following formulas:

$$\text{SMI (kg/m}^2\text{)} = \text{appendicular skeletal muscle mass index (kg)/height (m)}^2;$$

$$\text{BMI (kg/m}^2\text{)} = \text{weight (kg)/height (m)}^2$$

Sleep disturbance was measured using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI)^{14, 15}), which had been validated by Doi et al¹⁵). The PSQI is a self-report questionnaire that assesses the sleep quality of an individual over a 1-month interval. Self-reported items of the PSQI generate seven component scores (range of subscale scores, 0–3): sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction. The sum of the seven component scores yields one global score representing subjective sleep quality (range, 0–21) and the higher scores suggest worse sleep. Patients with total score >5 were classified as bad sleep^{14, 15}).

Information regarding age, gender, height, C-reactive protein (CRP), serum albumin value, cancer type, clinical stage, preoperative chemoradiotherapy, and comorbidity were obtained from patient medical records. In addition, information regarding education, drinking and smoking history, cognitive function, physical activity, depression, and nutritional status were collected using self-report questionnaires. Comorbidity was measured using the Charlson Comorbidity Index (CCI)¹⁶). The final CCI score was categorized into three grades and the sum of the weights assigned to 19 predetermined clinical conditions¹⁷). Cognitive function was measured using the Mini-Mental State Examination¹⁸), an interview-based test on cognitive ability. Accordingly, a score of <24 indicates cognitive impairment¹⁹). Physical activity was measured using the Japanese version of International Physical Activity Questionnaire Short Version²⁰), a self-report questionnaire that assesses physical activity within the last 7 days. Patients answered nine questions regarding walking frequency and duration, and frequency of moderate or vigorous physical activity. The total score was used to categorize patients into low, moderate, and high activity groups according to the guidelines²¹). Depression was measured using the Geriatric Depression Scale Short Version (GDS)²²). The total score ranged from 0 to 15 with a score of >5 indicating depression²³). Nutritional status was measured using the Mini Nutritional Assessment-Short Form (MNA-SF)²⁴), which evaluates six domains including anorexia, weight loss, mobility, psychological stress or acute disease, dementia or depression, and BMI, with scores ranging from 0 to 14 points. The total score was used to categorize patients into three groups: normal (MNA-SF: 12–14 points), at-risk (8–11 points), and malnourished (0–7 points)²⁵).

The Shapiro-Wilk test was performed to determine the normality of data. Characteristics of patients with and without low muscle mass were compared using Fisher’s exact tests, Student’s t-tests, or Mann-Whitney U tests. Bad sleep and PSQI subscales between those with and without low muscle mass were also compared using Fisher’s exact tests. Multiple logistic regression analyses were performed to determine the association between sleep disturbance and low muscle mass. Independent variables for logistic regression models included sleep factors that showed a significant relationship with the outcome (p<0.05) during univariate analysis. Covariate factors associated with the outcome (p<0.05) in univariate analyses

were included in the multivariate regression model. BMI has been excluded from our model considering the adjustment of BMI would result in over adjustment when investigating the association between sleep and muscle mass as suggested by the previous report²⁶. All analyses were conducted using EZR ver. 1.33²⁷ with $p < 0.05$ being considered statistically significant.

RESULTS

Patients' clinical characteristics are listed in Table 1. The average age of the participants was 70.5 years old (standard deviation=7.08; range=60–92 years), the majority of whom were men (84%) and had colorectal (40%) and gastric (38%) cancers. Among the 86 patients, 27 (31%) were identified as having low muscle mass. Patients with low muscle mass had significantly lower BMI (20.5 ± 2.35 vs. 24.6 ± 3.35 ; $p < 0.001$), higher CRP (1.22 ± 2.57 vs. 0.27 ± 0.64 ; $p = 0.020$), and more depressed ($p = 0.022$) than those without low muscle mass.

Table 2 shows the comparison of sleep disturbance between those with and without low muscle mass. A total of 39 patients (45%) experienced bad sleep. Moreover, those with low muscle mass had a significantly worse sleep quality ($p = 0.006$) than those without low muscle mass. Therefore, sleep quality was used as independent factors in the multiple logistic regression analyses. In accordance with the previous study⁹, sleep quality had been categorized into either “good” (fairly good or very good) or “bad” (fairly bad or very bad). Tables 3 shows the results for logistic regression analyses. After adjusting for CRP and GDS, the significant association between bad sleep quality and low muscle mass has been found (odds ratio, 4.15; 95% confidence interval, 1.02–16.9) (Table 3).

Table 1. Association between covariates and low muscle mass

	All (n=86)	Low muscle mass (n=27)	No low muscle mass (n=59)	p
Age* (years)	70.5 ± 7.08	71.6 ± 8.25	70.1 ± 6.50	0.62
Gender (males), n (%)	72 (84)	26 (96)	46 (78)	0.055
BMI* (kg/m ²)	23.3 ± 3.60	20.5 ± 2.35	24.6 ± 3.35	<0.001
Education* (years)	12.7 ± 2.60	12.4 ± 2.69	12.8 ± 2.56	0.54
CRP* (mg/dL)	0.57 ± 1.58	1.22 ± 2.57	0.27 ± 0.64	0.020
Serum Albumin* (g/dL)	3.89 ± 0.51	3.71 ± 0.57	3.97 ± 0.46	0.11
Cancer type				0.98
Gastric, n (%)	32 (37)	11 (41)	21 (36)	
Esophageal, n (%)	16 (19)	5 (19)	11 (19)	
Gastroesophageal junction, n (%)	4 (4.7)	1 (3.7)	3 (5.1)	
Colorectal, n (%)	34 (40)	10 (37)	24 (41)	
Clinical stage				1
0 – II, n (%)	64 (74)	20 (74)	44 (75)	
III – IV, n (%)	22 (26)	7 (26)	15 (25)	
Preoperative CRT, n (%)	20 (23)	6 (22)	14 (24)	1
CCI				0.91
CCI =0, n (%)	40 (47)	13 (48)	27 (46)	
CCI =1, n (%)	19 (22)	5 (19)	14 (24)	
CCI ≥2, n (%)	27 (31)	9 (33)	18 (31)	
MMSE <24, n (%)	13 (15)	7 (26)	6 (10)	0.10
History of drinking, n (%)	62 (72)	16 (59)	46 (78)	0.11
History of smoking, n (%)	62 (72)	23 (85)	39 (66)	0.076
IPAQ				0.51
Low, n (%)	26 (30)	10 (37)	16 (27)	
Moderate, n (%)	53 (62)	16 (59)	37 (63)	
High, n (%)	7 (8.1)	1 (3.7)	6 (10)	
GDS >5, n (%)	26 (30)	13 (48)	13 (22)	0.022
MNA-SF				0.077
Malnourished, n (%)	5 (5.8)	3 (11)	2 (3.4)	
At-risk, n (%)	32 (37)	13 (48)	19 (32)	
Normal, n (%)	49 (57)	11 (41)	38 (64)	

BMI: body mass index; CRP: C-reactive protein; CRT: chemoradiotherapy, CCI: Charlson Comorbidity Index; MMSE: Mini-Mental State Examination; IPAQ: International Physical Activity Questionnaire; GDS: Geriatric Depression Scale; MNA-SF: Mini Nutritional Assessment-Short Form.

Results are expressed as mean ± standard deviations or percentages.

Fisher's exact tests, Student's t-tests, and Mann-Whitney U tests were used for categorical, normally distributed, and non-normally distributed data, respectively.

*Mann-Whitney U tests.

Table 2. Association between PSQI components and low muscle mass

	All (n=86)	Low muscle mass (n=27)	No low muscle mass (n=59)	p
PSQI total score				
> 5	39 (45)	15 (56)	24 (41)	0.24
Sleep quality				0.006
Very good	11 (13)	5 (19)	6 (10)	
Fairly good	58 (67)	12 (44)	46 (78)	
Fairly bad	14 (16)	9 (33)	5 (8.5)	
Very bad	3 (3.5)	1 (3.7)	2 (3.4)	
Sleep latency				0.20
≤ 15 min	50 (58)	12 (44)	38 (64)	
16–30 min	25 (29)	10 (37)	15 (25)	
31–60 min	10 (12)	5 (19)	5 (8.5)	
> 60 min	1 (1.2)	0 (0)	1 (1.7)	
Sleep duration				0.98
≥ 7 h	31 (36)	10 (37)	21 (36)	
6–7 h	23 (27)	8 (30)	15 (25)	
5–6 h	30 (35)	9 (33)	21 (36)	
< 5 h	2 (2.3)	0 (0)	2 (3.4)	
Sleep efficiency				0.59
≥ 85%	57 (66)	18 (67)	39 (66)	
75–84%	15 (17)	3 (11)	12 (20)	
65–74%	11 (13)	5 (19)	6 (10)	
< 65%	3 (3.5)	1 (3.7)	2 (3.4)	
Sleep disturbances				0.11
0	13 (15)	1 (3.7)	12 (20)	
1–9	66 (77)	23 (85)	43 (73)	
10–18	7 (8.1)	3 (11)	4 (6.8)	
19–27	0 (0)	0 (0)	0 (0)	
Sleep medications				0.38
None	74 (86)	22 (81)	52 (88)	
Less than once per week	2 (2.3)	0 (0)	2 (3.4)	
Once or twice a week	3 (3.5)	2 (7.4)	1 (1.7)	
Three or more times a week	7 (8.1)	3 (11)	4 (6.8)	
Daytime dysfunction				0.56
0	59 (69)	17 (63)	42 (71)	
1–2	22 (26)	9 (33)	13 (22)	
3–4	5 (5.8)	1 (3.7)	4 (6.8)	
5–6	0 (0)	0 (0)	0 (0)	

PSQI: Pittsburg Sleep Quality Index.
Results expressed as absolute value and percentage.
Fisher's exact tests.

Table 3. Association between sleep quality and low muscle mass according to multiple logistic regression models

	Odds Ratio	95% Confidence Interval
CRP	1.89 [†]	1.06–3.37
GDS >5	1.74	0.48–6.25
Sleep quality		
Good sleep quality	1.00	
Bad sleep quality	4.15 [†]	1.02–16.9

[†]p<0.05.

CRP: C-reactive protein; GDS: Geriatric Depression Scale.

“Good sleep quality”, (fairly good or very good); “Bad sleep quality”, (fairly bad or very bad).

DISCUSSION

The purpose of this study was to investigate the relationship between sleep disturbance and low muscle mass in patients with gastrointestinal cancer scheduled for curative surgery. Our results revealed that bad sleep quality was significantly associated with low muscle mass after adjusting for CRP and GDS.

The results revealed the association between sleep quality assessed using PSQI subscales and muscle mass. Apart from the current study, several others have investigated the association between PSQI subscales and muscle mass. Buchmann et al. reported that sleep quality and latency were associated with muscle mass among community-dwelling elderly men, with results herein being similar in terms of sleep quality⁹. Bad sleep quality is common in patients with cancer²⁸. Moreover, sleep disorders may occur as a result of various factors, such as anxiety and distress regarding prognosis and treatment even for early-stage cancer¹². Therefore, our results support and expand those from previous studies in that sleep quality was found to be associated with muscle mass among patients with cancer whose symptoms were overlooked. In addition, the previous study reported that sleep quality was more strongly related to cognitive function regardless of sleep duration among older age people²⁹. Thus, bad sleep quality is a sleep disorder to be focused on among elderly people. Our study suggested that sleep quality plays an important role in maintaining muscle mass among patients with cancer.

A number of potential mechanisms mediate the association between sleep quality and muscle mass. A decline in sleep quality may prevent individuals from reaching slow-wave sleep (SWS), the deepest among the sleep stages³⁰. The release of growth hormone (GH), which is an anabolic hormone, has been shown to be the greatest during SWS³¹. Insulin-like Growth Factor 1 (IGF-1) is another anabolic hormone that is secreted predominantly by the liver in response to GH³². IGF-1 levels were found to be associated with the amount of time spent in SWS³³. Additionally, one study showed that experimentally fragmented sleep increased the levels of the catabolic hormone cortisol³⁰. Taken together, hormonal imbalances related to bad sleep quality might have been the cause for low muscle mass in the present study.

To the best of our knowledge, this has been the first study to examine the association between sleep disturbance and low muscle mass in patients with cancer. It is important to note that the present study focused on sleep disturbance in patients with cancer, which has received little attention. In addition, sleep disturbance was measured using the PSQI, which allowed the detailed investigation of the association between sleep disturbance and low muscle mass. The results showed that sleep quality was significantly associated with muscle mass. Nonetheless, some limitations of the present study need to be noted. First, given the cross-sectional nature of this study, we were unable to evaluate causality. Second, although some of the previous studies analyzed factors for low muscle mass within each gender^{9, 34}, the present study could not do the same due to the limited number of women included in our participants. Third, sleep information had been obtained through self-reporting instead of objective measures, such as polysomnography or actigraphy data. Therefore, further large-scale longitudinal studies involving both genders and objective measurements for sleep disturbance are needed.

The present study investigated the relationship between sleep disturbance and muscle mass in patients with gastrointestinal cancer scheduled for curative surgery. Accordingly, our results showed that bad sleep quality was associated with low muscle mass. The evaluation of sleep quality is crucial for addressing low preoperative muscle mass among patients with cancer since we cannot deny the possibility of the impact of sleep quality on the low muscle mass, which affects prognosis of patients with gastrointestinal cancer.

Presentation at a conference

We made the poster presentation in 12th World Congress of the International Society of Physical and Rehabilitation Medicine (ISPRM), ISPR8-2327.

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Conflict of interest

No author has declared conflicts of interest.

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