

Respiratory Muscle Weakness as a Risk Factor for Pneumonia in Older People

Tatsuma Okazaki^{a, b} Yoshimi Suzukamo^a Midori Miyatake^a Riyo Komatsu^c
Masahiro Yaekashiwa^d Mayumi Nihei^d Shinichi Izumi^{a, b, e} Takae Ebihara^f

^aDepartment of Physical Medicine and Rehabilitation, Tohoku University Graduate School of Medicine, Sendai, Japan; ^bCenter for Dysphagia of Tohoku University Hospital, Sendai, Japan; ^cDepartment of Respiratory Medicine, Hiraka General Hospital, Yokote, Akita, Japan; ^dDepartment of Respiratory Medicine, Sendai City Hospital, Sendai, Japan; ^eDepartment of Physical Medicine and Rehabilitation, Tohoku University Graduate School of Biomedical Engineering, Sendai, Japan; ^fDepartment of Geriatric Medicine, Kyorin University School of Medicine, Mitaka, Tokyo, Japan

Keywords

Respiratory muscles · Pneumonia · Aged people · Sarcopenia · Muscle strength

Abstract

Introduction: The respiratory muscle strength regulates the effectiveness of coughing, which clears the airways and protects people from pneumonia. Sarcopenia is an aging-related loss of muscle mass and function, the worsening of which is associated with malnutrition. The loss of respiratory and swallowing muscle strength occurs with aging, but its effect on pneumonia is unclear. This study aimed to determine the risks of respiratory muscle weakness on the onset and relapse of pneumonia in older people in conjunction with other muscle-related factors such as malnutrition. **Methods:** We conducted a longitudinal study with 47 pneumonia inpatients and 35 non-pneumonia controls aged 70 years and older. We evaluated the strength of respiratory and swallowing muscles, muscle mass, and malnutrition (assessed by serum albumin levels and somatic fat) during admission and

confirmed pneumonia relapse within 6 months. The maximal inspiratory and expiratory pressures determined the respiratory muscle strength. Swallowing muscle strength was evaluated by tongue pressure. Bioelectrical impedance analysis was used to evaluate the muscle and fat mass. **Results:** The respiratory muscle strength, body trunk muscle mass, serum albumin level, somatic fat mass, and tongue pressure were significantly lower in pneumonia patients than in controls. Risk factors for the onset of pneumonia were low inspiratory respiratory muscle strength (odds ratio [OR], 6.85; 95% confidence interval [CI], 1.56–30.11), low body trunk muscle mass divided by height² (OR, 6.86; 95% CI, 1.49–31.65), and low serum albumin level (OR, 5.46; 95% CI, 1.51–19.79). For the relapse of pneumonia, low somatic fat mass divided by height² was a risk factor (OR, 20.10; 95% CI, 2.10–192.42). **Discussion/Conclusions:** Respiratory muscle weakness, lower body trunk muscle mass, and malnutrition were risk factors for the onset of pneumonia in older people. For the relapse of pneumonia, malnutrition was a risk factor.

© 2021 The Author(s)
Published by S. Karger AG, Basel

Introduction

The number of deaths caused by pneumonia is increasing due to the aging of the population. Generally, an effective cough clears the airways and protects people from pneumonia [1, 2]. The respiratory muscle strength regulates the effectiveness of coughing [1, 3]. In addition to cough, the swallowing reflex plays an important role in preventing pneumonia in older people [4]. Several interventions have improved cough and swallowing reflexes such as the application of angiotensin-converting enzyme inhibitors and capsaicin [5–10]. However, among the factors that constitute the reflexes, previous intervention studies focused on their sensitivities but rarely investigated the muscle strength.

With aging, the loss of the skeletal muscle mass and function occurs, known as sarcopenia [11, 12]. Sarcopenia is diagnosed by the presence of both low muscle mass and function. Muscle function is evaluated by the muscle strength such as the handgrip strength or muscle performance such as gait speed [13]. Respiratory muscle strength is evaluated by the maximum static inspiratory and expiratory pressures that one can generate at the mouth [3]. The maximum static inspiratory and expiratory pressures are interpreted as the strength of the inspiratory and expiratory respiratory muscles, respectively [3]. The main inspiratory muscles are the diaphragm and the external intercostals [14, 15]. The main expiratory muscles are the abdominal muscles [3]. Strong inspiratory muscles produce deep preparatory inspiration, which is an integral part of an effective cough. The strength of expiratory muscles also determines the effectiveness of coughing [14, 16]. Thus, the main respiratory muscles are in the body trunk, and both the inspiratory and expiratory respiratory muscles are important to generate effective coughs.

Malnutrition is one of the mechanisms involved in the onset and process of sarcopenia [12]. The characteristics of malnutrition include low muscle mass, low BMI, low body fat mass, weight loss, and possibly low serum albumin levels [17, 18]. Recent weight loss was found to be a risk for developing pneumonia in community-dwelling older people [19], and a low serum albumin level was associated with the development of pneumonia among long-term hospitalized bedridden patients [20].

The strength and mass of swallowing muscles such as the tongue decrease with aging. These reductions are associated with impaired swallowing function [21, 22]. However, the association between swallowing muscle weakness and the development of pneumonia in older

people is presently not clear. Aging also reduces the strength of respiratory muscles [23].

As for the relationship between muscles and pneumonia, aspiration pneumonia induced muscle atrophy, and patients with low appendicular skeletal muscle mass showed poor survival rates [24, 25]. A study showed the potential of sarcopenia as a risk factor for the onset of pneumonia. However, for sarcopenia diagnosis, this study applied weaker cutoffs of muscle strength than the guidelines' recommendations [26].

Presently, we have only limited information about the relationship between respiratory muscle weakness and pneumonia in older people. This is also applicable for other muscle-related factors such as loss of respiratory muscle mass, loss of swallowing muscle strength, and sarcopenia. Malnutrition is associated with appendicular and swallowing muscle weakness [12, 21]. However, few previous studies evaluated respiratory muscle weakness in conjunction with malnutrition. The main objective of this study was to determine the unknown risks of respiratory muscle weakness in the onset and relapse of pneumonia in older people. Other objectives we addressed in this study were to identify risks of the abovementioned muscle-related factors in the onset and relapse of pneumonia. To achieve these objectives, we recruited older pneumonia patients and controls. We evaluated their respiratory muscles, swallowing muscle strength, sarcopenia, and nutritional status and confirmed pneumonia relapse within 6 months by a longitudinal study.

Materials and Methods

Study Design and Participants

Individuals aged 70 years and older admitted for pneumonia to a geriatric ward in Kyorin University Hospital or a respiratory ward in Sendai City Hospital were recruited from April 2018 to March 2019. Controls were non-pneumonia individuals admitted to the geriatric ward in Kyorin University Hospital or a respiratory ward in Sendai City Hospital for chronic diseases such as heart failure and were recruited from April 2018 to March 2019. A longitudinal study was conducted focusing on the above participants. Before the admission, all participants were dwelling in the community or nursing homes. Exclusion criteria were patients with advanced dementia, interstitial pneumonia, ventilation-associated pneumonia, postoperative pneumonia, tracheostomy, sepsis, bedridden state, cancer, dentures, and supine position. Since inflammation induces muscle atrophy [27], controls with infectious diseases such as urinary tract infection were also excluded. Relapse of pneumonia or survival within 6 months after the admission was confirmed by an interview with the patients' family conducted by phone. The human subjects institutional review boards in Sendai City Hospital, Sendai, the Tohoku University Ethics Committee, Sendai, and the Kyorin University Ethics Committee, Tokyo, Japan, approved the protocol.

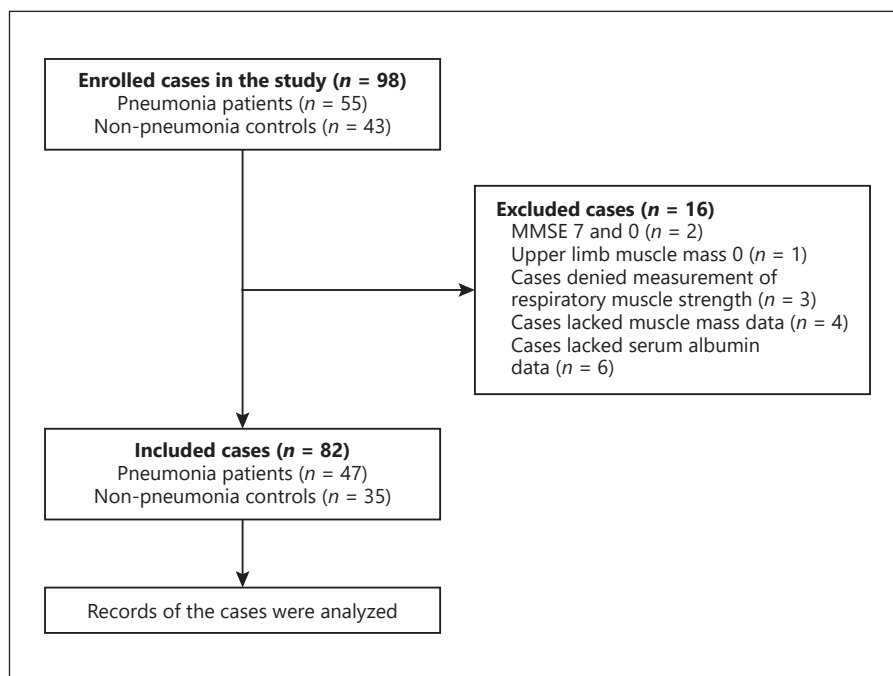


Fig. 1. A schematic diagram outlining the pneumonia patients and non-pneumonia controls selection process. MMSE, Mini-Mental State Examination.

Assessment of Muscle Strength and Body Composition

Respiratory muscle strength was determined by measuring the maximal inspiratory and expiratory pressures as recommended by the American Thoracic Society and the European Respiratory Society [3]. Hand-held multifunctional spirometers with pressure-sensing transducers were used (HI-801, CHEST M.I., Inc., Tokyo, Japan). Participants were instructed to take a deep breath and to seal their lips tightly around the mouthpiece. They were instructed to maximally expire and inspire before maximal inspiratory and expiratory pressure measurements, respectively. Handgrip strength was measured using portable electronic hand-held dynamometers (Corvette Inc., Wakayama, Japan). Tongue pressure was measured by an instrument with a small balloon connected to a pressure-sensing transducer (JMS, Hiroshima, Japan) [22]. Subjects were instructed to maximally press a balloon to their palates using their tongues. Gait speed was evaluated by measuring the time for walking 6 m. We evaluated muscle mass and body fat mass by bioelectrical impedance analysis (Inbody S10, Inbody, Seoul, Korea). Patients with low handgrip strength and/or low gait speed accompanied by low muscle mass were diagnosed as sarcopenic according to the Asian Working Group for Sarcopenia criteria [13]. Cutoff values were handgrip strength <26 kg for men and <18 kg for women; gait speed ≤ 0.8 m/s; appendicular skeletal muscle mass/height² <7.0 kg/m² for men and <5.7 kg/m² for women. The above indices were evaluated after recovery from patients' acute condition, generally, between 6 and 10 days after their admission.

Evaluation of Comprehensive Geriatric Assessment

We evaluated cognitive impairment using the Mini-Mental State Examination (MMSE) in Japanese, which has a 30-point scale with lower scores indicating greater cognitive impairment [28]. Activity of daily living (ADL) status was assessed by the Barthel Index, which ranges from 0 to 100 [8]. Swallowing function was

evaluated by a modified water-swallowing test [29–31]. Briefly, 3.0 mL of cold water was placed under the tongue and the patients were instructed to swallow. Swallowing was identified by visual observation of laryngeal movement. The test was conducted 3 times, and the worst swallowing activity was taken. People with the assessment criteria 1–3 shown below were diagnosed as having impaired swallowing function: (1) unable to swallow and with choking and/or breathing changes; (2) swallow but with changes in breathing; (3) swallow but with choking and/or wet hoarseness. Body height was calculated from the individual length of the knee height to avoid the effect of vertebral osteoporosis [32]. Knee height, weight, and serum albumin levels were examined at the time of admission. Other assessments and measures were performed between 6 and 10 days after the admission.

Definition of Pneumonia

Pneumonia was diagnosed by the presence of new radiographic lung infiltrates on X-ray and/or computed tomography plus at least 2 or 3 clinical features (leukocytosis or leukopenia, fever >38°C, and purulent secretions) [33].

Statistical Analysis

To estimate risk factors for the onset of pneumonia, the baseline characteristics of pneumonia patients and controls were compared. Paired *t* tests for continuous variables and the χ^2 test for categorical variables were performed, respectively. Continuous variables were selected based on the results of an univariate analysis conducted at a significance level of <0.05, and receiver operating characteristic (ROC) curve analysis was performed to convert categorical variables to be used as independent variables. ROC analysis was performed since clinical cutoff values of older people for indices evaluated in this study such as respiratory muscle strengths were not clear. Multivariate logistic regression models

calculated odds ratio (OR) and 95% confidence intervals (CIs) after adjusting potential confounders. To determine the risk factors for pneumonia relapse, only the pneumonia patients were analyzed. Similar procedures to analyze the risk factors for the onset of pneumonia were performed. The characteristics of non-surviving pneumonia patients were analyzed in a manner similar to the procedures for relapsed pneumonia patients. The required sample size to detect the effect size 0.5 between 2 groups by *t* test was 49 for each group, with an 80% power and 5% significance for a 1-sided test. All data were analyzed by SPSS software, version 24.0 (IBM Corp., Armonk, NY, USA). The sample size was calculated by G*Power 3.1.9.2. *p* values <0.05 were considered significant.

Results

Fifty-five pneumonia patients and 43 non-pneumonia controls were enrolled in the study. Two patients with MMSE 7 and 0 were excluded due to the low reliability in the measurement of respiratory muscle strength. One patient with an upper limb muscle mass 0 was excluded due to the expectation of a detection error. Three patients refused measurement of the respiratory muscle strength. Two patients and 2 controls lacked muscle mass data. Six controls lacked serum albumin data. Finally, 47 pneumonia patients (male, *n* = 30) and 35 controls (male, *n* = 22) were analyzed (Fig. 1).

Table 1 lists the characteristics of the older pneumonia patients and controls. The inspiratory maximum static pressure was weaker in the older pneumonia patients than in the older controls without pneumonia (mean [SD], 16.4 [10.9] vs. 24.7 [9.7]; *p* = 0.001). The expiratory maximum static pressure showed a similar result (21.3 [14.4] vs. 31.0 [14.8]; *p* = 0.004). The tongue pressure, which was interpreted as the swallowing muscle strength, was weaker in the pneumonia patients than in the controls (13.6 [8.2] vs. 19.5 [9.2]; *p* = 0.004). Body trunk muscle mass divided by height² was lower in the patients than in the controls (5.5 [1.1] vs. 6.6 [1.5]; *p* = 0.001). The percentage of people with impaired swallowing function was greater in the pneumonia patients than in the controls (impaired swallowing function 51.1 vs. 17.1%; *p* = 0.002). These results suggest loss of respiratory muscle strength and body trunk muscle mass, weak tongue pressure, and impaired swallowing function in the older pneumonia patients.

As for nutrition, the serum albumin level (2.9 [0.6] vs. 3.6 [0.6]; *p* = 0.000), BMI (19.5 [3.9] vs. 21.7 [3.7]; *p* = 0.013), total muscle mass divided by height² (14.0 [2.5] vs. 15.1 [1.9]; *p* = 0.027), and somatic fat mass divided by height² (4.3 [2.5] vs. 5.8 [2.6]; *p* = 0.008) were lower in the pneumonia patients than in the controls. These findings

suggest poorer nutritional status in older pneumonia patients than in controls. The percentage of people with sarcopenia was not different between the pneumonia patients and the controls (56.5 vs. 37.1%; *p* = 0.116). The number of comorbidities was not different between the pneumonia patients and the controls (2.7 [0.8] vs. 2.2 [1.4]; *p* = 0.063). Among the comorbidities, the percentage of people with lung disease (31.9 vs. 11.4%; *p* = 0.036) and heart disease (48.9 vs. 22.9%; *p* = 0.021) was greater in pneumonia patients than in controls. We evaluated ADL by the Barthel Index. A lower Barthel Index in the pneumonia patients than in the controls suggested worse ADL in the patients than in the controls (65.3 [36.3] vs. 80.4 [25.0]; *p* = 0.029).

A multivariate logistic regression model adjusted for age and gender showed that a low maximum static inspiratory pressure (OR, 6.85; 95% CI, 1.56–30.11; *p* = 0.011), low body trunk muscle mass divided by height² (OR, 6.86; 95% CI, 1.49–31.65; *p* = 0.014), and low serum albumin level (OR, 5.46; 95% CI, 1.51–19.79; *p* = 0.010) were risk factors for the onset of pneumonia (*R*² = 0.605, Table 2). Another multivariate model, exchanging maximum static inspiratory pressure for expiratory pressure, showed low maximum static expiratory pressure (OR, 4.31; 95% CI, 1.11–16.67; *p* = 0.034) and impaired swallowing function (OR, 4.79; 95% CI, 1.10–20.87; *p* = 0.037) as risk factors for the onset of pneumonia in addition to low body trunk muscle mass divided by height² and low serum albumin level (*R*² = 0.585, see online suppl. Table 1; see www.karger.com/doi/10.1159/000514007 for all online suppl. material). Other models, such as by exchanging maximum static inspiratory pressure for tongue pressure, or the presence of sarcopenia, showed that neither low tongue pressure (*R*² = 0.614, online suppl. Table 2) nor presence of sarcopenia (data not shown) was a risk factor. The albumin level has been reported to mainly reflect the degree of catabolism/inflammation rather than the nutritional status [17, 18]. Therefore, we adjusted the albumin level and other variables by the leukocyte count as an indicator of inflammation and exchanged them with the variables in Table 2. In addition, we included the ADL as a variable. A multivariate model showed that the adjusted albumin level (OR, 7.02; 95% CI, 1.70–29.04; *p* = 0.007) was still a risk factor for the onset of pneumonia, whereas the ADL was not (*R*² = 0.629, online suppl. Table 3). A low maximum static inspiratory pressure (OR, 6.77; 95% CI, 1.38–33.19; *p* = 0.018) and low body trunk muscle mass divided by height² (OR, 5.21; 95% CI, 1.06–25.47; *p* = 0.042) were also risk factors for the onset of pneumonia. These results suggest that respiratory muscle weak-

Table 1. The characteristics of the pneumonia and the control groups at baseline ($n = 82$)

Variable ^a	Overall ($n = 82$)	Pneumonia ($n = 47$)	Control ($n = 35$)	p value [†]
Age, years	85.7±5.6	86.5±5.5	84.5±5.6	0.108
Sex				
Male	52 (63.4)	30 (63.8)	22 (62.9)	1.000
Female	30 (36.6)	17 (36.2)	13 (37.1)	
ADL (Barthel Index)	71.8±32.7	65.3±36.3	80.4±25.0	0.029
Cognition (MMSE)	22.6±4.7	21.8±5.2	23.7±3.6	0.078
Number of comorbidities	2.5±1.1	2.7±0.8	2.2±1.4	0.081
Diabetes mellitus	19 (23.2)	7 (14.9)	12 (34.3)	0.063
Heart disease	31 (37.8)	23 (48.9)	8 (22.9)	0.021
Hypertension	56 (68.3)	34 (72.3)	22 (62.9)	0.472
Lung disease	19 (23.2)	15 (31.9)	4 (11.4)	0.036
Stroke/epilepsy	32 (39.0)	21 (44.7)	11 (31.4)	0.258
Sarcopenia				
Positive	38 (48.1)	26 (56.5)	13 (37.1)	0.116
Negative	42 (51.9)	20 (43.5)	22 (62.9)	
Modified water-swallowing test				
1–3 (impaired)	30 (36.6)	24 (51.1)	6 (17.1)	0.002
4–5 (normal)	52 (63.4)	23 (48.9)	29 (82.9)	
Power indicators				
PImax, cm H ₂ O	19.9±11.2	16.4±10.9	24.7±9.7	0.001
PEmax, cm H ₂ O	25.4±15.3	21.3±14.4	31.0±14.8	0.004
Tongue pressure, kPa	16.2±9.1	13.6±8.2	19.5±9.2	0.004
Muscle mass indicators, kg/m ²				
Total muscle mass	14.5±2.3	14.0±2.5	15.1±1.9	0.027
Appendicular muscle mass	6.6±1.5	6.4±1.6	6.9±1.3	0.121
Body trunk muscle mass	6.0±1.4	5.5±1.1	6.6±1.5	0.001
Nutrition indicators				
Albumin, g/dL	3.2±0.7	2.9±0.6	3.6±0.6	0.000
BMI, kg/m ²	20.4±4.0	19.5±3.9	21.7±3.7	0.013
Somatic fat mass, kg/m ²	4.9±2.6	4.3±2.5	5.8±2.6	0.008

ADL, activity of daily living; MMSE, Mini-Mental State Examination; PImax, maximum static inspiratory pressure; PEmax, maximum static expiratory pressure. [†] p values were determined by paired 2-sample t test or χ^2 test. ^a Data represented as mean \pm SD, or n (%).

ness, low body trunk muscle mass, and low serum albumin level were risk factors for the onset of pneumonia in older people.

All the pneumonia patients recovered and were discharged from the hospitals. However, among 47 pneumonia patients, 20 had relapses of pneumonia within the following 6 months. Relapsed patients showed lower somatic fat mass divided by height² (3.4 [1.8] vs. 4.9 [2.7]; $p = 0.047$) and greater numbers of comorbidities (3.0 [0.8] vs. 2.4 [0.8]; $p = 0.028$) than non-relapsed patients (Table 3). A multivariate model adjusted for age and gender showed that low somatic fat mass divided by height² was a risk factor for the relapse of pneumonia (OR, 20.10; 95% CI, 2.10–192.42; $p = 0.009$; $R^2 = 0.433$, Table 4). These re-

Table 2. Logistic regression model to show risk factors for pneumonia^{a, b}

	OR	95% CI	p value
PImax	6.85	1.56–30.11	0.011
Body trunk muscle mass	6.86	1.49–31.65	0.014
Modified water-swallowing test	3.35	0.79–14.33	0.102
Albumin	5.46	1.51–19.79	0.010

OR, odds ratio; PImax, maximum static inspiratory pressure. Cutoff values: PImax, 20.0 cm H₂O; body trunk muscle mass, 6.4 kg/m²; albumin, 3.3 g/dL. ^a Adjusted for age and gender. ^b $R^2 = 0.605$.

Table 3. The characteristics of the relapse and the non-relapse groups at baseline ($n = 47$)

Variable ^a	Overall ($n = 47$)	Relapse group ($n = 20$)	Non-relapse group ($n = 27$)	p value [†]
Age, years	86.5±5.5	88.0±5.9	85.4±5.0	0.109
Sex				
Male	30 (63.8)	14 (70.0)	16 (59.3)	0.546
Female	17 (36.2)	6 (30.0)	11 (40.7)	
ADL (Barthel Index)	65.3±36.3	55.8±41.5	72.4±30.8	0.140
Cognition (MMSE)	21.8±5.2	20.4±6.7	22.9±3.5	0.128
Number of comorbidities	2.7±0.8	3.0±0.8	2.4±0.8	0.028
Sarcopenia				
Positive	26 (56.5)	13 (65.0)	13 (50.0)	0.377
Negative	20 (43.5)	7 (35.0)	13 (50.0)	
Modified water-swallowing test				
1–3 (impaired)	24 (51.1)	13 (65.0)	11 (40.7)	0.142
4–5 (normal)	23 (48.9)	7 (35.0)	16 (59.3)	
Power indicators				
PI _{max} , cm H ₂ O	16.4±10.9	15.3±12.2	17.2±10.0	0.578
PE _{max} , cm H ₂ O	21.3±14.4	20.2±15.5	22.1±13.8	0.652
Tongue pressure, kPa	13.6±8.2	13.5±7.6	13.7±8.9	0.942
Muscle mass indicators				
Total muscle mass, kg/m ²	14.0±2.5	14.0±2.0	14.0±2.9	0.970
Appendicular muscle mass, kg/m ²	6.4±1.6	6.1±1.7	6.6±1.5	0.313
Body trunk muscle mass, kg/m ²	5.5±1.1	5.4±0.8	5.6±1.4	0.739
Nutrition indicators				
Albumin, g/dL	2.9±0.6	2.8±0.6	3.0±0.6	0.160
BMI, kg/m ²	19.5±3.9	18.7±3.0	20.1±4.5	0.195
Somatic fat mass, kg/m ²	4.3±2.5	3.4±1.8	4.9±2.7	0.047

ADL, activity of daily living; MMSE, Mini-Mental State Examination; PI_{max}, maximum static inspiratory pressure; PE_{max}, maximum static expiratory pressure. [†] p values were determined by paired 2-sample t test or χ^2 test. ^a Data represented as mean \pm SD, or n (%).

Table 4. Logistic regression model to show risk factors for pneumonia relapse^{a, b}

	OR	95% CI	p value
Somatic fat mass	20.10	2.10–192.42	0.009
Number of comorbidities	2.44	0.90–6.59	0.078

OR, odds ratio. Cutoff values: somatic fat mass, 5.4 kg/m².
^a Adjusted for age and gender. ^b $R^2 = 0.433$.

sults suggest that low somatic fat mass can induce relapses of pneumonia in older people.

Among 47 pneumonia patients, 9 did not survive the following 6 months. Table 5 lists the characteristics of surviving and non-surviving pneumonia patients. The non-survivors showed weaker inspiratory maximum static pressure (9.3 [4.9] vs. 18.0 [11.3]; $p = 0.001$) and

poorer nutritional status than survivors. When the ROC curve divided the data into 2 groups, all the data of non-survivors were in the worse group such as maximum static inspiratory pressure, serum albumin level, somatic fat mass, and BMI. Thus, we could not apply a multivariate model to analyze risk factors for non-survivors.

Discussion

Weakened inspiratory and expiratory muscle strengths were risk factors for the onset of pneumonia, which suggests their inability to generate effective coughing to clear airways. Another risk factor, low body trunk muscle mass, suggests a loss of respiratory muscle mass due to the distribution. Malnutrition was a risk factor for both the onset and relapse of pneumonia. As far as we know, this is the first study that showed an association between respi-

Table 5. The characteristics of the survivors and the non-survivors at baseline ($n = 47$)

Variable ^a	Overall ($n = 47$)	Non-survivors ($n = 9$)	Survivors ($n = 38$)	p value [†]
Age, years	86.5±5.5	88.7±5.4	86.0±5.4	0.191
Sex				
Male	30 (63.8)	7 (77.8)	23 (60.5)	0.455
Female	17 (36.2)	2 (22.2)	15 (39.5)	
ADL (Barthel Index)	65.3±36.3	36.1±38.1	72.2±32.6	0.006
Cognition (MMSE)	21.8±5.2	16.2±6.4	23.2±3.9	0.012
Number of comorbidities	2.7±0.8	2.9±0.6	2.6±0.8	0.256
Sarcopenia				
Positive	26 (56.5)	7 (77.8)	19 (51.4)	0.262
Negative	20 (43.5)	2 (22.2)	18 (48.6)	
Modified water-swallowing test				
1–3 (impaired)	24 (51.1)	8 (88.9)	16 (42.1)	0.023
4–5 (normal)	23 (48.9)	1 (11.1)	22 (57.9)	
Power indicators				
PI _{max} , cm H ₂ O	16.4±10.9	9.3±4.9	18.0±11.3	0.001
PE _{max} , cm H ₂ O	21.3±14.4	13.9±8.3	23.0±15.1	0.089
Tongue pressure, kPa	13.6±8.2	12.1±5.8	14.0±8.8	0.538
Muscle mass indicators				
Total muscle mass, kg/m ²	14.0±2.5	13.3±0.7	14.1±2.8	0.096
Appendicular muscle mass, kg/m ²	6.4±1.6	5.5±1.0	6.6±1.7	0.053
Body trunk muscle mass, kg/m ²	5.5±1.1	5.5±0.9	5.5±1.2	0.958
Nutrition indicators				
Albumin, g/dL	2.9±0.6	2.6±0.5	3.0±0.6	0.037
BMI, kg/m ²	19.5±3.9	17.3±2.0	20.0±4.1	0.009
Somatic fat mass, kg/m ²	4.3±2.5	2.7±1.8	4.6±2.5	0.029

ADL, activity of daily living; MMSE, Mini-Mental State Examination; PI_{max}, maximum static inspiratory pressure; PE_{max}, maximum static expiratory pressure. [†] p values were determined by paired 2-sample t test or χ^2 test. ^a Data represented as mean \pm SD, or n (%).

ratory muscle weakness and the onset of pneumonia in older people. Moreover, this study showed the unfavorable effects of malnutrition on the onset and relapse of pneumonia in older people. These findings suggest the therapeutic potential of the respiratory muscles and malnutrition as targets of pneumonia management in older people.

The definition of sarcopenia was revised in 2019 [34]. We planned this study in 2017 based on the European Consensus of the definition of sarcopenia before its revision [12]. The revised guideline emphasizes the importance of muscle weakness rather than the muscle mass for the diagnosis of sarcopenia [34]. Accordingly, the association between respiratory muscle weakness and the onset of pneumonia was a major finding in this study.

A previous study reported an association between respiratory muscle weakness and mortality in community-dwelling older people [35]. However, the biological basis

for this association was not clear. Taken together with our findings, this association might be due to the high susceptibility to pneumonia in older people with respiratory muscle weakness. For effective coughing, the deeper the inspiration, the stronger the cough intensity. Expiratory muscles also play important role in cough intensity. Thus, both the inspiratory and expiratory muscles regulate the effectiveness of coughing [14].

We revealed a poorer nutritional status in pneumonia patients than in controls by serum albumin level, BMI, and somatic fat mass divided by height². In addition, guidelines state that low muscle mass is another characteristic of malnutrition. Therefore, low total muscle mass and body trunk muscle mass divided by height² in pneumonia patients in this study may emphasize their poor nutritional status. Since the albumin level also reflects the degree of catabolism/inflammation, we adjusted the albumin level with the leukocyte count. The multivariate

model showed that the adjusted albumin level was still a risk factor for the onset of pneumonia. Thus, we use and interpret the albumin level as an indicator of malnutrition with caution [17, 18]. Overall, the above findings suggest the importance of the nutritional status in the onset and relapse of pneumonia in older people.

Among the factors that define sarcopenia, the value of the appendicular skeletal muscle mass divided by height² was not different between the older pneumonia patients and the controls. When we chose patients that we measured handgrip strength, this subclass analysis showed that the handgrip strength was not different between older pneumonia patients ($n = 42$) and controls ($n = 35$). Thus, in muscle mass and strength, there were discrepancies between appendicular skeletal and respiratory muscles in older pneumonia patients. This can be partially explained by previous studies that reported poor correlations between weakness of the diaphragm and appendicular skeletal muscles in severely ill patients [36].

Previous studies suggested the effects of ethnic differences and aging on the respiratory muscle strength [23, 37]. Divided into several groups by age, average respiratory muscle strength of Japanese was 58–76% of that of age-matched Swiss people [38]. The mean age of patients in our study was 85.7, and little is known about the respiratory muscle strength of older people aged 85 and over. Further studies might be required for accumulating data of respiratory muscle strength from older people of various ethnicities to obtain cutoff values for future studies.

The main risk factors for pneumonia in older people suggested by previous studies were chronic lung disease, chronic heart disease, malnutrition, and aspiration [19, 39–42]. To identify risk factors for the onset of pneumonia, we once included lung disease and heart disease as variables in a multivariate model. However, we could not complete the analysis due to the small numbers of control patients with these diseases in this study. In online suppl. Table 1, we detected impaired swallowing function as a risk factor for the onset of pneumonia. This suggests aspiration as a risk factor for the onset of pneumonia in addition to malnutrition in this study.

This study has several limitations. We could not measure the respiratory muscle strength of patients with very low MMSE. Thus, we excluded patients with advanced dementia in this study. We recruited patients from 2 hospitals in Japan, but the participants were all Japanese. We recruited older pneumonia patients, but we did not distinguish between first-onset and relapsed pneumonia patients. Therefore, the data were from both first-onset and relapsed patients. We evaluated pneumonia relapse by

phone interview with the patients' family. The diagnosis of pneumonia was according to the information that the patient's family obtained from the physician in charge at the moment. Thus, we did not diagnose the pneumonia relapse. We calculated the required sample size and recruited the participants accordingly. However, the size was limited. This low number of patients might limit the conclusions for pneumonia relapse and survival. Since previous studies could not show an association between the severity of pneumonia and its relapse, we did not investigate the severity. For analyzing risk factors for relapses of pneumonia, we recruited older pneumonia patients. In general, they showed weakened respiratory muscle strength and reduced body trunk muscle mass. Hence, there is a possibility that malnutrition was a risk factor for relapse of pneumonia among older people with weakened respiratory muscle strength and low body trunk muscle mass. To further analyze the role of muscles in pneumonia relapse, we may have to recruit older pneumonia patients with normal levels of respiratory muscle strength and body trunk muscle mass, if possible. The main causative diseases for the admission of controls were heart disease (mainly heart failure), epilepsy, stroke, diabetes mellitus, and lung disease (mainly bronchial asthma and chronic obstructive pulmonary disease). We planned to evaluate the muscle indices when the controls and pneumonia patients were in a similar clinical condition. We assumed that patients were in a stable condition when they recovered from their severe illness. Therefore, we evaluated the muscle indices after their recovery. However, we could not exclude the possible influence of the causative diseases for admission on the data.

In conclusion, this study suggests that weakened respiratory muscle strength, lower body trunk muscle mass, and malnutrition were risk factors for the onset of pneumonia in older people. In addition, malnutrition was a risk factor for the relapse of pneumonia. These findings suggest that the respiratory muscles, with loss of strength and possibly mass accompanied by malnutrition, can manage gas exchange, but cannot afford extra efforts such as generating effective coughing to protect older people from pneumonia.

Acknowledgements

We thank Brent Bell for reading the manuscript and Mikiko Fuda for advice. We also thank Kumiko Nagai, Mami Shouji, and Koichi Kozaki for their technical assistance and advice. This manuscript has not been published previously or considered for publication concurrently in another publication.

Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Subjects or their guardians have given their written informed consent. The human subjects institutional review boards in Sendai City Hospital, Sendai, the Tohoku University Ethics Committee, Sendai, and the Kyorin University Ethics Committee, Tokyo, Japan, approved the protocol (2017-1-341, 710).

Conflict of Interest Statement

The authors declare no competing financial interests.

References

- 1 Ebihara S, Sekiya H, Miyagi M, Ebihara T, Okazaki T. Dysphagia, dystussia, and aspiration pneumonia in elderly people. *J Thorac Dis.* 2016 Mar;8(3):632–9.
- 2 Okazaki T, Ebihara S, Mori T, Izumi S, Ebihara T. Association between sarcopenia and pneumonia in older people. *Geriatr Gerontol Int.* 2020 Jan;20(1):7–13.
- 3 American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med.* 2002 Aug 15;166(4):518–624.
- 4 Almirall J, Rofes L, Serra-Prat M, Icart R, Palomera E, Arreola V, et al. Oropharyngeal dysphagia is a risk factor for community-acquired pneumonia in the elderly. *Eur Respir J.* 2013 Apr;41(4):923–8.
- 5 Ebihara T, Sekizawa K, Nakazawa H, Sasaki H. Capsaicin and swallowing reflex. *Lancet.* 1993 Feb 13;341(8842):432.
- 6 Ebihara T, Sekizawa K, Ohru T, Nakazawa H, Sasaki H. Angiotensin-converting enzyme inhibitor and danazol increase sensitivity of cough reflex in female guinea pigs. *Am J Respir Crit Care Med.* 1996 Feb;153(2):812–9.
- 7 Sekizawa K, Matsui T, Nakagawa T, Nakayama K, Sasaki H. ACE inhibitors and pneumonia. *Lancet.* 1998 Sep 26;352(9133):1069.
- 8 Ebihara T, Takahashi H, Ebihara S, Okazaki T, Sasaki T, Watando A, et al. Capsaicin troche for swallowing dysfunction in older people. *J Am Geriatr Soc.* 2005 May;53(5):824–8.
- 9 Ebihara T, Ebihara S, Maruyama M, Kobayashi M, Itou A, Arai H, et al. A randomized trial of olfactory stimulation using black pepper oil in older people with swallowing dysfunction. *J Am Geriatr Soc.* 2006 Sep;54(9):1401–6.
- 10 Ebihara T, Ebihara S, Watando A, Okazaki T, Asada M, Ohru T, et al. Effects of menthol on the triggering of the swallowing reflex in elderly patients with dysphagia. *Br J Clin Pharmacol.* 2006 Sep;62(3):369–71.
- 11 Rosenberg IH. Sarcopenia: origins and clinical relevance. *J Nutr.* 1997 May;127(5 Suppl):990S–991S.

Funding Sources

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of the Japanese Government to T.O. (No. 26461176 and 18K08133) and T.E. (No. 19152637). This research was supported by AMED (under Grant No. 17dk0110024) to T.O. and T.E., and a research grant from the General Insurance Association of Japan to T.O.

Author Contributions

T.O. and T.E. designed the work, collected and analyzed data, and wrote the manuscript. Y.S. and M.M. analyzed and interpreted data and revised the manuscript. R.K., M.Y., and M.N. collected and analyzed the data. S.I. designed and revised the manuscript.

- 21 Fujishima I, Fujiu-Kurachi M, Arai H, Hyodo M, Kagaya H, Maeda K, et al. Sarcopenia and dysphagia: position paper by four professional organizations. *Geriatr Gerontol Int.* 2019 Feb;19(2):91–7.
- 22 Mori T, Izumi S, Suzukamo Y, Okazaki T, Iketani S. Ultrasonography to detect age-related changes in swallowing muscles. *Eur Geriatr Med.* 2019;10(5):753–60.
- 23 Evans JA, Whitelaw WA. The assessment of maximal respiratory mouth pressures in adults. *Respir Care.* 2009 Oct;54(10):1348–59.
- 24 Maeda K, Akagi J. Muscle mass loss is a potential predictor of 90-day mortality in older adults with aspiration pneumonia. *J Am Geriatr Soc.* 2017 Jan;65(1):e18–22.
- 25 Komatsu R, Okazaki T, Ebihara S, Kobayashi M, Tsukita Y, Nihei M, et al. Aspiration pneumonia induces muscle atrophy in the respiratory, skeletal, and swallowing systems. *J Cachexia Sarcopenia Muscle.* 2018 Aug;9(4):643–53.
- 26 Altuna-Venegas S, Aliaga-Vega R, Maguiña JL, Parodi JF, Runzer-Colmenares FM. Risk of community-acquired pneumonia in older adults with sarcopenia of a hospital from Callao, Peru 2010–2015. *Arch Gerontol Geriatr.* 2019 May–Jun;82:100–5.
- 27 Okazaki T, Liang F, Li T, Lemaire C, Daniahou G, Shoelson SE, et al. Muscle-specific inhibition of the classical nuclear factor- κ B pathway is protective against diaphragmatic weakness in murine endotoxemia. *Crit Care Med.* 2014 Jul;42(7):e501–9.
- 28 Watando A, Ebihara S, Ebihara T, Okazaki T, Takahashi H, Asada M, et al. Daily oral care and cough reflex sensitivity in elderly nursing home patients. *Chest.* 2004 Oct;126(4):1066–70.
- 29 Tohara H, Saitoh E, Mays KA, Kuhlemeier K, Palmer JB. Three tests for predicting aspiration without videofluorography. *Dysphagia.* 2003;18(2):126–34.

- 30 Teramoto S, Fukuchi Y, Sasaki H, Sato K, Sekizawa K, Matsuse T, et al. High incidence of aspiration pneumonia in community- and hospital-acquired pneumonia in hospitalized patients: a multicenter, prospective study in Japan. *J Am Geriatr Soc*. 2008 Mar;56(3):577–9.
- 31 Murakami K, Hirano H, Watanabe Y, Eda-hiro A, Ohara Y, Yoshida H, et al. Relationship between swallowing function and the skeletal muscle mass of older adults requiring long-term care. *Geriatr Gerontol Int*. 2015 Oct;15(10):1185–92.
- 32 Chumlea WC, Roche AF, Steinbaugh ML. Estimating stature from knee height for persons 60 to 90 years of age. *J Am Geriatr Soc*. 1985 Feb;33(2):116–20.
- 33 American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. 2005 Feb 15;171(4):388–416.
- 34 Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing*. 2019 Jul 1;48(4):601.
- 35 Buchman AS, Boyle PA, Wilson RS, Gu L, Bienias JL, Bennett DA. Pulmonary function, muscle strength and mortality in old age. *Mech Ageing Dev*. 2008 Nov;129(11):625–31.
- 36 Petrof BJ. Diaphragm weakness in the critically ill: basic mechanisms reveal therapeutic opportunities. *Chest*. 2018 Dec;154(6):1395–403.
- 37 Johan A, Chan CC, Chia HP, Chan OY, Wang YT. Maximal respiratory pressures in adult Chinese, Malays and Indians. *Eur Respir J*. 1997 Dec;10(12):2825–8.
- 38 Kamide N, Ogino M, Yamashina N, Fukuda M. Sniff nasal inspiratory pressure in healthy Japanese subjects: mean values and lower limits of normal. *Respiration*. 2009;77(1):58–62.
- 39 Hanson LC, Weber DJ, Rutala WA. Risk factors for nosocomial pneumonia in the elderly. *Am J Med*. 1992 Feb;92(2):161–6.
- 40 Riquelme R, Torres A, El-Ebiary M, de la Bel-lacasa JP, Estruch R, Mensa J, et al. Community-acquired pneumonia in the elderly: a multivariate analysis of risk and prognostic factors. *Am J Respir Crit Care Med*. 1996 Nov;154(5):1450–5.
- 41 Vila-Corcoles A, Ochoa-Gondar O, Rodriguez-Blanco T, Raga-Luria X, Gomez-Bertomeu F, Group ES. Epidemiology of community-acquired pneumonia in older adults: a population-based study. *Respir Med*. 2009 Feb;103(2):309–16.
- 42 Manabe T, Teramoto S, Tamiya N, Okochi J, Hizawa N. Risk factors for aspiration pneumonia in older adults. *PLoS One*. 2015;10(10):e0140060.