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Respiratory Muscle Strength as a Predictor of Exacerbations in Patients With Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background and Objective: Chronic obstructive pulmonary disease (COPD) is closely related to skeletal muscle dysfunction, and the evaluation of respiratory muscle function has recently been recommended. We aimed to investigate the effects of respiratory muscle dysfunction on clinical outcomes.

Methods: We retrospectively reviewed the medical records of patients with COPD whose respiratory muscle strength was measured between June 2015 and December 2021. We then analysed the effects of respiratory muscle strength on moderate-to-severe exacerbations after adjusting for confounding factors, including sex, age, forced expiratory volume in 1-s percent predicted, hand grip strength, and skeletal muscle mass index. We also compared the temporal relationship between respiratory and systemic skeletal muscle dysfunctions.

Results: Respiratory muscle weakness (RMW) was observed in 48.1% (100) of the 208 patients. Low percent predicted maximal inspiratory pressure was an independent risk factor for moderate-to-severe exacerbations within 1 year in the Cox regression analysis (adjusted hazard ratio per 1 standard deviation increase, 0.521; 95% confidence interval, 0.317–0.856). Approximately half of the patients already exhibited RMW at the mild systemic skeletal muscle dysfunction, while those with sarcopenia had higher RMW rates. More patients with RMW experienced progressive systemic skeletal muscle dysfunction within 1 year compared to those without RMW.

Conclusion: Lower respiratory muscle strength is associated with an increased risk of exacerbation. Respiratory muscle function could serve as a marker of disease status and early prognosis in COPD.

1 | Introduction

Chronic obstructive pulmonary disease (COPD) is a complex lung condition primarily characterised by airflow obstruction owing to emphysema and bronchiolitis [1]. Among its various manifestations, patients often suffer from skeletal muscle dysfunction caused by systemic inflammation, nutritional disorders, and reduced physical activity [2–5]. Impairment in skeletal

Abbreviations: %FEV_1, forced expiratory volume in 1-s percent predicted; %PImax, percent predicted PImax; 6MWD, 6-min walk distance; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HGS, handgrip strength; HR, hazard ratio; mMRC, modified Medical Research Council; PEmax, maximal expiratory pressure; PImax, maximal inspiratory pressure; RMW, respiratory muscle weakness; SD, standard deviation; SMI, skeletal muscle mass index.

Summary

- Evaluation of respiratory muscle function is recommended for patients with COPD.
- Our results suggest that lower respiratory muscle strength is associated with an increased risk of exacerbations.
- Respiratory muscle function could serve as a marker of disease status and early prognosis in COPD.

muscle strength and mass was reported to have a poor prognosis leading to reduced quality of life, increased exacerbations, and mortality [6–8]. The evaluation of respiratory muscle function has recently been recommended because respiratory muscles are not only part of the skeletal muscles but are also involved in the respiratory system. The inspiratory muscles, primarily the diaphragm, serve as the principal drivers of ventilation and are essential for optimal pulmonary function [9]. By contrast, expiration is normally a passive process secondary to the active phase of inspiration. Consequently, maximal inspiratory pressure (PImax) was regarded as a more relevant and practical parameter for evaluating respiratory muscle function. Previous studies have shown that respiratory muscle function correlates with dyspnoea, pulmonary function, and exercise tolerance [10–12]. These findings suggest a relationship between respiratory muscle function and the pathophysiology of COPD. However, there is a lack of studies analysing the effects of respiratory muscle dysfunction on clinical outcomes in patients with COPD in a time-course manner. Only two studies have reported that patients with frequent exacerbations had lower respiratory muscle strength than stable patients [13, 14]. Moreover, because these were cross-sectional studies, they did not fully demonstrate a causal relationship between respiratory muscle strength and exacerbations in COPD.

Furthermore, the relationship between systemic and respiratory muscle dysfunctions has not yet been thoroughly explored. Sarcopenia is a progressive, systemic skeletal muscle disorder. It has been reported that sarcopenia worsens clinical outcomes in patients with COPD [7]; at the same time, it remains unclear whether respiratory muscle dysfunction precedes systemic sarcopenia or vice versa.

We hypothesized that lower respiratory muscle strength is associated with increased exacerbations. This retrospective cohort study aimed to investigate the effects of PImax, a marker of respiratory muscle strength, on moderate-to-severe exacerbations in patients with COPD. In addition, we aimed to clarify the temporal relationship between respiratory and systemic skeletal muscle dysfunctions.

2 | Methods

2.1 | Study Design and Patients

We conducted a retrospective cohort study using the medical records of the Osaka City University Hospital from June 2015 to December 2021. This study included outpatients with COPD whose respiratory muscle strength was measured at the Osaka City University Hospital. During the study period, depending on the clinical determination by respiratory physicians, all outpatients underwent respiratory muscle strength measurement along with other tests for a comprehensive assessment of their condition unless they could not tolerate the tests due to severe cardiovascular diseases or mobility impairments. Diagnoses of COPD were confirmed according to the Global Initiative for Chronic Obstructive Lung Disease guidelines [1]. We excluded patients with only one visit and insufficient information on systemic skeletal muscles. We also excluded patients with combined interstitial fibrosis exhibiting patterns of usual interstitial pneumonia, nonspecific interstitial pneumonia, or unclassifiable patterns on chest computed tomography (CT) according to the international multidisciplinary classification system for idiopathic interstitial pneumonias proposed in 2013 [15]. This study was performed in accordance with the Declaration of Helsinki. This human study was approved by the Ethics Committee of the Osaka Metropolitan University Graduate School of Medicine-approval: 2023-127. The patient's informed consent was waived for the retrospective nature of the study, and we used an opt-out method so that patients and families could refuse to participate in the study.

2.2 | Body Mass Index, Severity of Dyspnoea, and Comorbidities

Body mass index (BMI) was calculated using the formula: weight/height [2] (kg/m^2). We used the modified Medical Research Council (mMRC) scale to evaluate dyspnoea with scores from 0 to 4 [1]. We evaluated comorbidities commonly referenced in studies on sarcopenia, including dyslipidemia, chronic kidney disease, cerebrovascular disease, and osteoporosis [16–19].

2.3 | Measurements of Respiratory Muscle Strength

We measured PImax using a spirometer with an optional respiratory muscle strength sensor (HI-801; Chest Co. Ltd., Tokyo, Japan) to assess participants' respiratory muscle strength. Additionally, maximal expiratory pressure (PEmax) was measured during the same test series. The PImax manoeuvre was performed at the residual volume, whereas the PEmax manoeuvre was performed at the total lung capacity [20]. The maximum value was recorded when the difference was less than 20% in the three measurements. We calculated the percent predicted PImax (%PImax) based on a reported predictive equation incorporating sex, age, height, and weight [21]. This equation was developed based on data from healthy Japanese participants. Respiratory muscle weakness (RMW) was defined as %PImax $< 70\%$ because the median %PImax was 70.5% in our study, and previous studies have adopted this cut-off [12, 22].

2.4 | Measurements of Skeletal Muscle Function

We measured skeletal muscle strength and mass to assess systemic skeletal muscle function. Skeletal muscle strength was

measured using the handgrip strength (HGS) test conducted with a Smedley Hand Dynamometer (Matsumiya Medical Products Co. Ltd., Tokyo, Japan). The measurement was performed twice bilaterally with the elbow extended and the underarm and wrist in a neutral position. The highest values were then recorded. Skeletal muscle mass was measured by the skeletal muscle mass index (SMI) calculated using the bioelectrical impedance analysis (InBody3.0 instrument Biospace Co. Ltd., Seoul, South Korea) [23]. The SMI was calculated using the formula: (appendicular skeletal muscle mass)/height [2] (kg/m^2). According to the 2019 Asian Working Group for Sarcopenia guidelines, we defined patients with both low muscle strength and low muscle mass as having sarcopenia [24]. Low muscle strength was defined as HGS < 28 kg in male patients and < 18 kg in female patients. The low muscle mass threshold was defined as SMI < 7.0 kg/m^2 in male patients and < 5.7 kg/m^2 in female patients.

2.5 | 6-Minute Walk Test and Pulmonary Function Test

The 6-minute walk test (6MWT) was performed to objectively assess exercise capacity. This test measured the distance a patient could walk at a quick pace on a flat, hard surface in 6 min. Pulmonary function was assessed using spirometry (CHESTAC-8900; Chest M.I. Inc., Tokyo, Japan). The 6MWT and pulmonary function test were performed according to the American Thoracic Society and European Respiratory Society guidelines [25, 26].

2.6 | Clinical Outcome

The primary endpoint was onset of moderate or severe exacerbation. COPD exacerbation is defined as an event characterised by increased dyspnoea and/or cough and sputum that worsens in < 14 days, which may be accompanied by tachypnoea and/or tachycardia [1]. Moderate exacerbation requires treatment with systemic steroids and/or antibiotics, while severe exacerbation requires emergency room visits or hospitalisation [1].

2.7 | Statistical Analysis

Patients were categorised into two groups: the RMW and non-RMW groups. Continuous variables were expressed as medians and quartiles, and categorical variables were described as frequencies in the between-group comparison. We performed the Student's T-test to compare continuous variables between the two groups, and the Chi-square test or Fisher's exact test to compare categorical variables. We evaluated the effects of respiratory muscle strength on COPD prognosis using a Kaplan–Meier curve for exacerbation-free probability and a Cox regression model. Time zero was defined as the day of respiratory muscle strength measurement, and observation was censored at transfer to another hospital, death from causes other than COPD, or 1 year from initiation. We identified forced expiratory volume in 1-s percent predicted ($\%FEV_1$) as a confounding factor because pulmonary function correlates with respiratory muscle function and influences exacerbations [10, 11, 27]. Other factors, including sex, age, HGS, and SMI, were also selected based on previous reports [6, 7, 28, 29]. Adjusted hazard ratio (HR) for standardised %PImax was used in the Cox regression model, along with 95% confidence intervals (CIs). We conducted a further analysis using the subset data of patients with available past exacerbation records to investigate the impact of respiratory muscle strength on exacerbations adjusted for the prior year's exacerbation [30]. To investigate the temporal relationship between RMW and systemic sarcopenia, we compared the frequency of baseline RMW and changes in systemic skeletal muscle strength and mass. The frequency of RMW was evaluated in the four groups according to HGS and SMI: normal HGS and normal SMI; normal HGS and low SMI; low HGS and normal SMI and low HGS and low SMI. We performed the Chi-square test to compare the proportions of RMW between the groups. Changes in systemic skeletal muscle strength and mass were assessed in each group with and without RMW in a dataset of patients with measured values available 1 year from the initiation, with a range of 3 months before and after, using a Sankey diagram. We depicted the transitions among the four groups divided by HGS and SMI. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using the EZR software (Jichi Medical University, Saitama, Japan) [31].

3 | Results

3.1 | Patient Characteristics

Among the 208 patients with COPD, 100 had RMW (Table 1). Patients with RMW were more likely to have severe dyspnoea, low pulmonary function, and exercise intolerance than those without RMW. The prevalence of sarcopenia was also higher in the RMW group. Out of the 208 patients, data on past exacerbations for the previous year was available for 111 patients. In this subset, 26.1% of the patients with RMW experienced exacerbations in the prior year, while those without RMW experienced a rate of 20.0%. The mean follow-up duration was 320.8 days. Regarding the breakdown of 184 censored cases, 55 patients were transferred to other hospitals, one patient died, and 128 patients completed the one-year follow-up. The cause of death in the deceased patient was unknown; therefore, this case was not counted as an event.

3.2 | Association Between Baseline Respiratory Muscle Strength and Exacerbation

Twenty-four patients experienced exacerbations in 1 year, comprising 13 moderate and 11 severe exacerbations. In the RMW group, 17.0% (17 out of 100) suffered exacerbations: 9 were classified as moderate and 8 as severe. On the other hand, 6.5% (7 out of 108) in the non-RMW group suffered exacerbations: 4 were classified as moderate and 3 as severe. The adjusted Kaplan–Meier curve showed that participants with RMW had more exacerbations than those without RMW (Figure 1). Multivariate analysis revealed that an increase in %PImax led to a significant decrease in the hazard ratio for COPD exacerbation (adjusted HR per 1 standard deviation (SD) increase, 0.521; 95% CI, 0.317–0.856) after adjustment for confounding factors (sex, age, $\%FEV_1$, HGS, and SMI) (Table 2). Subgroup

TABLE 1 | Patients' characteristics according to respiratory muscle strength.

Variables	All patients ($n=208$)	Patients without RMW ($n=108$)	Patients with RMW ($n=100$)	p value
Male	180 (86.5%)	94 (87.0%)	86 (86.0%)	0.988
Age (year)	72.0 (66.0–77.0)	71.0 (65.0–77.0)	72.5 (66.8–76.3)	0.984
BMI (kg/m^2)	22.7 (19.8–24.5)	23.0 (20.7–24.9)	21.7 (18.7–24.4)	0.024*
Smoking status (pack-year)	48.0 (32.8–78.0)	45.0 (30.0–75.3)	50.0 (38.2–80.0)	0.582
Inhaled corticosteroid use	53 (25.5%)	29 (26.9%)	24 (24.0%)	0.750
Oral corticosteroid use	2 (1.0%)	2 (1.9%)	0 (0.0%)	0.498
Comorbidity				
Dyslipidemia	41 (19.7%)	22 (20.4%)	19 (19.0%)	0.941
Chronic kidney disease	24 (11.5%)	13 (12.0%)	11 (11.0%)	0.987
Cerebrovascular disease	13 (6.3%)	8 (7.4%)	5 (5.0%)	0.667
Osteoporosis	11 (5.3%)	4 (3.7%)	7 (7.0%)	0.360
mMRC 0/1/2/3/4	58 (27.9%) /71 (34.1%) /46 (22.1%) /25 (12.0%) /8 (3.8%)	36 (33.3%) /43 (39.8%) /20 (18.5%) /7 (6.5%) /2 (1.9%)	22 (22.0%) /28 (28.0%) /26 (26.0%) /18 (18.0%) /6 (6.0%)	0.007*
6MWD (m)	420.0 (370.0–480.0)	445.0 (390.0–496.3)	400.0 (337.5–450.0)	<0.001*
%FEV$_1$ (%)	72.3 (54.1–89.0)	78.3 (61.6–91.0)	67.1 (47.7–85.9)	0.001*
PImax (cmH$_2$O)	52.1 (34.3–67.1)	67.0 (56.0–83.8)	33.7 (26.3–42.2)	<0.001*
PEmax (cmH$_2$O)	63.8 (48.7–82.3)	70.2 (56.5–87.0)	59.9 (41.4–75.0)	<0.001*
HGS (kgf)	31.0 (25.0–36.0)	32.0 (26.0–37.0)	30.0 (23.8–36.0)	0.267
SMI (kg/m^2)	7.8 (7.0–8.5)	7.9 (7.2–8.5)	7.7 (6.8–8.3)	0.210
Sarcopenia	21 (10.1%)	5 (4.6%)	16 (16.0%)	0.010*

Variables	Patients with available data on past exacerbations ($n=111$)	Patients without RMW ($n=65$)	Patients with RMW ($n=46$)	p value
Past exacerbation history	25 (22.5%)	13 (20.0%)	12 (26.1%)	0.599

Note: Data are presented as median (first-third quartile) or n (%).
Abbreviations: %FEV$_1$, forced expiratory volume in 1-s percent predicted; 6MWD, 6-min walk distance; BMI, body mass index; HGS, handgrip strength; mMRC, modified Medical Research Council; PEmax, maximal expiratory pressure; PImax, maximal inspiratory pressure; RMW, respiratory muscle weakness; SMI, skeletal muscle mass index.
*p value <0.05.

analysis divided by exacerbation severity showed a similar trend: the adjusted HR for %PImax was 0.571 per 1 SD increase (95% CI, 0.295–1.11) for moderate exacerbations and 0.465 (95% CI, 0.210–1.03) for severe exacerbations. Additionally, a subset analysis of patients with available past exacerbation records showed that %PImax can predict exacerbations in the next year (adjusted HR per 1 SD increase, 0.407; 95% CI, 0.202–0.820) even after adjusting for the prior year's exacerbation history (Table 3). Considering that smoking status can affect COPD exacerbations, Cox regression analyses were conducted, incorporating this variable into Table 2 and Table 3 for sensitivity analysis. The analysis had similar results: (Tables S1 and S2 in the Supporting Information).

3.3 | Proportion of Patients With RMW in the Four Groups Classified by Systemic Skeletal Muscle Strength and Mass

RMW was observed in 76.2% (16/21) of the patients with sarcopenia (Figure 2). Among patients without sarcopenia, RMW was observed in 45.4% (59/130) of those with normal HGS and normal SMI, in 42.1% (16/38) of those with normal HGS and low SMI, and in 47.4% (9/19) of those with low HGS and normal SMI. Sarcopenia showed higher RMW rates, compared to normal HGS and normal SMI ($p=0.017$), normal HGS and low SMI ($p=0.025$), low HGS and normal SMI ($p=0.120$). However, RMW was present in nearly half of the patients, even in the absence of systemic sarcopenia.

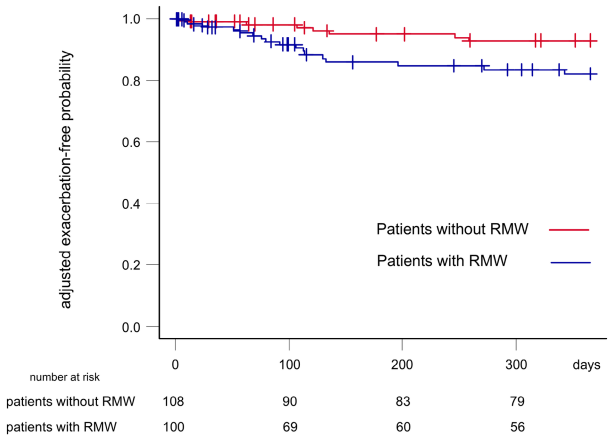

FIGURE 1 | Kaplan–Meier curve for exacerbation-free probability among groups with and without RMW adjusted for sex, age, %FEV_1, HGS, and SMI. The red and blue curves represent adjusted exacerbation-free probability for patients without and with RMW, respectively. The group with RMW had more exacerbations than that without RMW in 1 year. %FEV_1, forced expiratory volume in 1-s percent predicted; HGS, handgrip strength; RMW, respiratory muscle weakness; SMI, skeletal muscle mass index.

TABLE 2 | Cox regression model of COPD exacerbation risk for %PImax adjusted by sex, age, %FEV_1, HGS, and SMI.

Covariates	Adjusted HR (95% CI)	*p* value
%PImax (per 1 SD increase)	0.521 (0.317–0.856)	0.010*
Female (vs. male)	2.59 (0.718–9.31)	0.146
Age (per 1 year increase)	0.968 (0.918–1.02)	0.213
%FEV_1 (per 1% increase)	0.992 (0.976–1.01)	0.299
HGS (per 1 kgf increase)	0.990 (0.930–1.05)	0.751
SMI (per 1 kg/m^2 increase)	0.935 (0.666–1.31)	0.696

Abbreviations: %FEV_1, forced expiratory volume in 1-s percent predicted; %PImax, percent predicted maximal inspiratory pressure; CI, confidential interval; HGS, handgrip strength; HR, hazard ratio; SD, standard deviation; SMI, skeletal muscle mass index.
*p value < 0.05.

It remains unclear whether respiratory muscle dysfunction precedes systemic muscle dysfunction, or if both progress in parallel. To demonstrate the trajectory of sarcopenia and non-sarcopenia between the clusters stratified by respiratory muscle function at baseline and 1 year, a Sankey diagram was created.

3.4 | Changes in Systemic Skeletal Muscle Function After 1 Year According to Respiratory Muscle Strength

Of the 208 patients, 37 had available follow-up data on systemic skeletal muscle (Figure 3). Of these, 18 were categorised as having RMW. Three patients in the RMW group exhibited decreased systemic skeletal muscle strength and mass. By contrast, only one patient in the non-RMW group experienced progression of systemic skeletal muscle dysfunction.

TABLE 3 | Cox regression model of COPD exacerbation risk for %PImax adjusted by sex, age, %FEV_1, HGS, SMI, and exacerbation history in the previous year.

Covariates	Adjusted HR (95% CI)	*p* value
%PImax (per 1 SD increase)	0.407 (0.202–0.820)	0.012*
Female (vs. male)	1.28 (0.217–7.52)	0.786
Age (per 1 year increase)	0.955 (0.889–1.03)	0.210
%FEV_1 (per 1% increase)	0.989 (0.970–1.01)	0.266
HGS (per 1 kgf increase)	1.02 (0.957–1.09)	0.509
SMI (per 1 kg/m^2 increase)	0.885 (0.508–1.54)	0.666
Exacerbation history (vs. no exacerbation)	5.04 (1.57–16.2)	0.007*

Abbreviations: %FEV_1, forced expiratory volume in 1-s percent predicted; %PImax, percent predicted maximal inspiratory pressure; CI, confidential interval; HGS, handgrip strength; HR, hazard ratio; SD, standard deviation; SMI, skeletal muscle mass index.
*p value < 0.05.

4 | Discussion

In this study, we identified important clinical findings. Lower respiratory muscle strength is associated with an increased risk of exacerbation. Our results revealed that the evaluation of respiratory muscle function could predict outcomes in patients with COPD, suggesting that respiratory muscles could be a novel target for COPD interventions.

To the best of our knowledge, this is the first study to demonstrate that respiratory muscle dysfunction independently increases the risk of exacerbations. COPD exacerbations have a negative impact on disease progression and prognosis, with prior exacerbations increasing the risk of future relapses [1, 30]. In this study, we focused on exacerbations as an early clinical outcome to explore their association with respiratory muscle dysfunction. Some studies have shown that respiratory muscle function correlates with dyspnoea, pulmonary function, and exercise tolerance [10–12]. Others have shown that systemic skeletal muscle dysfunction negatively affects clinical outcomes and increases the risk of exacerbation [6–8]. However, no cohort study has investigated the effect of respiratory muscle dysfunction on exacerbations. Our study revealed that the evaluation of respiratory muscle strength can aid in identifying patients with a higher risk of exacerbations, potentially leading to better survival and prognosis through early detection and treatment of exacerbations [1, 32].

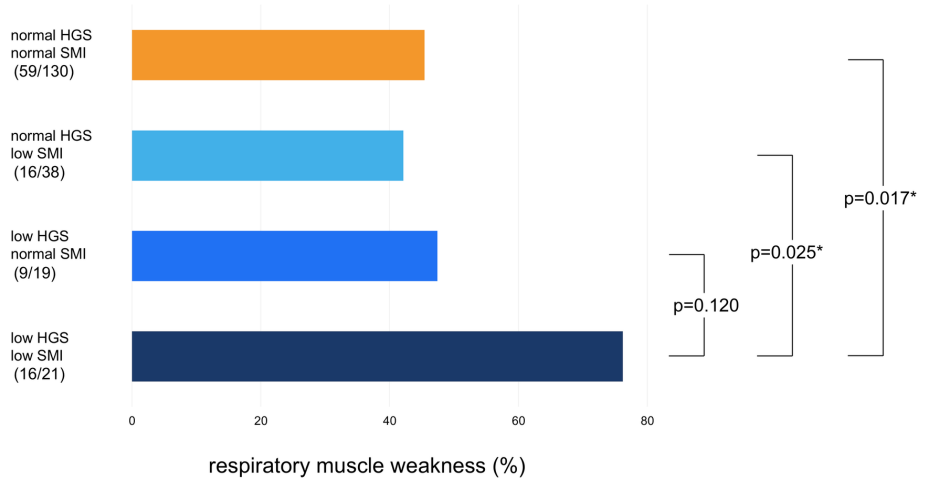

FIGURE 2 | The proportion of patients with RMW in each group classified by systemic skeletal muscle function. The sarcopenia group exhibited higher RMW rates compared to the other groups. However, RMW was present in nearly half of the patients, even in the absence of systemic sarcopenia. HGS, handgrip strength; RMW, respiratory muscle weakness; SMI, skeletal muscle mass index. *p value < 0.05.

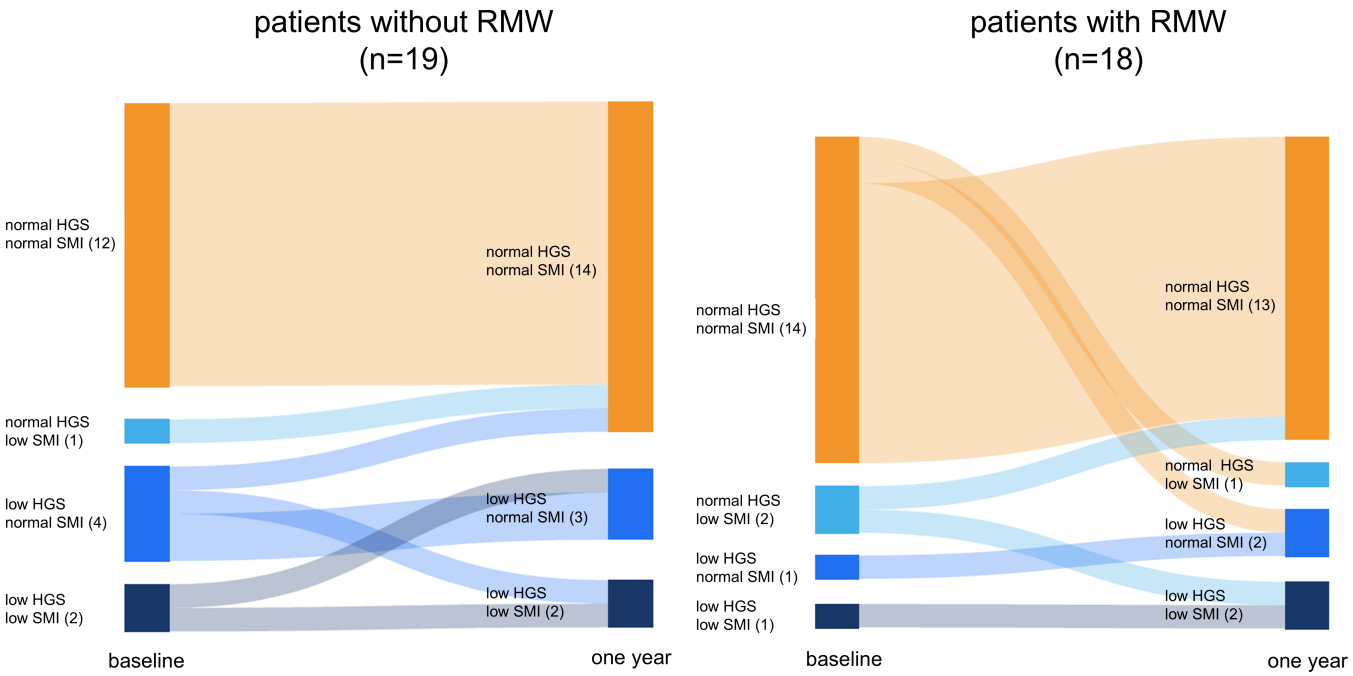

FIGURE 3 | Sankey diagram showing the systemic skeletal muscle function change from baseline to 1 year according to respiratory muscle strength. Three patients in the RMW group exhibited decreased systemic skeletal muscle strength or mass in 1 year. Only one patient experienced progression of systemic skeletal muscle dysfunction in the group without RMW. HGS, handgrip strength; RMW, respiratory muscle weakness; SMI, skeletal muscle mass index.

In this study, we specifically focused on respiratory muscle strength. We adopted the concept used for the assessment of respiratory sarcopenia, which highlights the interaction between respiratory and systemic skeletal muscle dysfunction [33, 34]. According to this concept, measuring respiratory muscle strength is essential for assessing respiratory sarcopenia [34]. Respiratory muscle mass is also a crucial parameter, and low pectoralis muscle in COPD gene and low erector spinae muscle in COPD as measured on CT scans have already been reported to be associated with increased mortality [35, 36]. These reports indicate the importance of respiratory muscle mass and strength in COPD. In our study, we chose to evaluate respiratory muscle strength alone for a simpler baseline assessment because measuring respiratory muscle mass is sometimes challenging due to the lack of a standardised methodology and cut-off values [33, 34], and respiratory muscle strength is currently considered the most reliable measure of respiratory muscle function [37].

Some speculated mechanisms could explain the association between respiratory muscle strength and the development of acute exacerbations of COPD. Reduced respiratory muscle strength leads to poor clearance of secretions, resulting in lower airway microbial colonisation and local inflammation [38–40]. It decreases physical activity, leading to decreased resting inspiratory

capacity and increased dynamic hyperinflation during exercise [41, 42]. Moreover, decline in respiratory muscle strength can also hinder adequate drug distribution and deposition in the airways, thereby weakening pharmacotherapeutic efficacy and promoting disease progression in COPD [43]. Respiratory muscle strength appears to play an upstream role in the worsening of COPD. Considering these mechanisms and our findings that respiratory muscle dysfunction increases exacerbation risk, interventions focused on respiratory muscle strength could be key in preventing COPD progression.

Another important finding of our study is that respiratory muscle dysfunction might precede systemic skeletal muscle dysfunction. Figure 2 shows that a considerable number of patients with COPD already exhibited RMW at the mild systemic skeletal muscle dysfunction stage, although RMW was more common in patients with comorbid systemic sarcopenia. Moreover, although the analysed subset comprised a small sample size with potential selective bias, Figure 3 shows that the RMW group had more patients with progressive systemic skeletal muscle dysfunction in 1 year than the non-RMW group.

Respiratory muscle dysfunction has been reported to be caused by several factors and biological mechanisms common to systemic sarcopenia [44]. A previous study showed that respiratory muscles are more susceptible to damage than peripheral muscles and sensitively reflect disease progression in patients with COPD [45]. Furthermore, respiratory muscle dysfunction is correlated with low exercise capacity [12], which could lead to systemic muscle dysfunction. In view of these mutual biological mechanisms, different vulnerabilities, and observed correlations, our results suggest the possibility that respiratory muscles are affected at an earlier stage than systemic skeletal muscles in patients with COPD. Our results also suggest respiratory muscle dysfunction might predict the subsequent development of systemic skeletal muscle dysfunction.

Given our findings that lower respiratory muscle strength is associated with an increased risk of exacerbation and that respiratory muscle dysfunction might precede systemic skeletal muscle dysfunction, inspiratory muscle training (IMT) to improve respiratory muscle strength could reduce exacerbations and improve COPD prognosis. Pulmonary rehabilitation (PR) has been reported to be beneficial for exacerbation and muscle functions, however, some reports have not shown the benefits [46, 47]. The training programs of PR are diverse. From our perspective, respiratory muscle dysfunction might precede systemic sarcopenia, suggesting that focusing on IMT could be an important factor. IMT reduces dyspnoea and improves exercise tolerance, although IMT alone is not strongly recommended [1, 47]. Furthermore, it is not widely used in clinical practice because the selection criteria and load settings are yet to be identified. Additional research is required to demonstrate that improving respiratory muscle strength helps prevent exacerbations and systemic skeletal muscle dysfunction.

Our study had some limitations. First, our primary analysis did not account for the potential impact of past exacerbation history and nutritional status [30, 48]. This was because our study was based on a retrospective cohort design, and 97 patients (46.6%) were first-time consultations at our outpatient clinic; therefore, we did not have access to their past records related to these factors. Nevertheless, the result of supplementary analysis of patients with available past exacerbation records suggests that respiratory muscle strength is a risk factor for exacerbations in the following year, regardless of previous exacerbation history, even with inevitable selective bias. Second, RMW was defined as %PImax < 70% according to the median value in this study and previous reports [12, 22]; however, a clear cut-off for determining low respiratory muscle strength is yet to be found. Further studies with larger sample sizes or comparisons with healthy controls are needed to determine the exact cut-off value. Nevertheless, our study revealed that %PImax was an independent predictor of COPD exacerbation as a continuous variable in the Cox proportional hazards model. This result is noteworthy, regardless of the cut-off setting. Third, we did not assess respiratory muscle mass. Respiratory muscle mass has been measured using ultrasound and CT images [34, 49], although the evaluation methods and threshold values are yet to be fully standardised. However, quantifying the respiratory muscle mass will increase the potential for a more comprehensive evaluation of respiratory function. Fourth, some exacerbations could have been missed if patients received treatment at other hospitals.

In conclusion, respiratory muscle dysfunction negatively affects clinical outcomes in patients with COPD. Our results suggest that lower respiratory muscle strength is associated with an increased risk of exacerbations, which might precede systemic skeletal muscle dysfunction. Respiratory muscle function could serve as a marker of disease status and early prognosis in COPD. Further prospective cohort studies are warranted to elucidate this beneficial role of respiratory muscle function.

Author Contributions

Yuichiro Furukawa: conceptualization (lead), data curation (lead), formal analysis (lead), investigation (lead), methodology (lead), project administration (lead), writing – original draft (lead). **Atsushi Miyamoto:** conceptualization (lead), data curation (lead), formal analysis (lead), investigation (lead), methodology (lead), project administration (lead), validation (lead), writing – original draft (lead), writing – review and editing (lead). **Kazuhisa Asai:** conceptualization (lead), data curation (lead), formal analysis (lead), investigation (lead), methodology (lead), project administration (lead), validation (lead), writing – review and editing (lead). **Masaya Tsutsumi:** writing – review and editing (equal). **Kaho Hirai:** writing – review and editing (equal). **Takahiro Ueda:** writing – review and editing (equal). **Erika Toyokura:** writing – review and editing (equal). **Misako Nishimura:** data curation (equal), investigation (equal), writing – review and editing (equal). **Kanako Sato:** data curation (equal), investigation (equal), writing – review and editing (equal). **Kazuhiro Yamada:** data curation (equal), investigation (equal), writing – review and editing (equal). **Tetsuya Watanabe:** data curation (equal), investigation (equal), validation (lead), writing – review and editing (lead). **Tomoya Kawaguchi:** project administration (equal), writing – review and editing (equal).

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Ethics Statement

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by the Ethics Committee of the Osaka Metropolitan University Graduate School of Medicine-approval:

2023-127. The patient's informed consent was waived for the retrospective nature of the study, and we used an opt-out method so that patients and families could refuse to participate in the study.

Conflicts of Interest

Kazuhisa Asai is an Editorial Board member of Respirology and a co-author of this article. He was excluded from all editorial decision-making related to the acceptance of this article for publication. The other authors have no conflicts of interest to declare.

Data Availability Statement

The data that supports the findings of this study are available in the Supporting Information of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.