

# FFMI: A Pivotal Indicator Bridging Pulmonary, Sleep, and Systemic Factors in COPD–OSA Overlap Patients

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**Objective:** Overlap Syndrome (OVS), combining Chronic Obstructive Pulmonary Disease (COPD) and Obstructive Sleep Apnea (OSA), is common yet often unrecognized. This study aims to compare the Fat - Free Mass Index (FFMI) between OVS and simple COPD patients and analyze subgroup differences in OVS for better early identification and severity assessment.

**Methods:** Clinical data of 364 patients (203 in COPD group, 161 in OVS group) were analyzed regarding clinical features, pulmonary function, sleep apnea, etc. The OVS group was divided into low-FFMI and normal-FFMI subgroups (the cutoff value of FFMI < 17kg/m<sup>2</sup>) for correlation analysis.

**Results:** Statistically significant differences in frequency of acute exacerbations and hospitalizations in the past year, and comorbidities were observed between the COPD group and OVS group (all  $p < 0.05$ ). The OVS group exhibited significantly lower FEV<sub>1</sub>% pred, FEV<sub>1</sub> /FVC, 6MWT, FFMI, and L-SaO<sub>2</sub> compared to the COPD group (all  $p < 0.05$ ), while AHI, ESS, CAT, and MMRC were higher. Patients with lower FFMI demonstrated lower FEV<sub>1</sub>%pred, FEV<sub>1</sub>/FVC, L-SaO<sub>2</sub>, and 6MWT than those with normal FFMI. Additionally, AHI, MMRC, frequency of acute exacerbations, and hospitalizations in the past year were higher (all  $p < 0.05$ ) in this group. Correlation analysis revealed that in the OVS group, FFMI positively correlated with FEV<sub>1</sub>%pred and FEV<sub>1</sub>/FVC, and negatively with AHI, MMRC, exacerbation/hospitalization frequency.

**Conclusion:** OVS patients had distinct features like more exacerbations, and lower lung function. The OVS subgroup with different FFMI showed significant differences in lung function and sleep indices. FFMI is closely related to pulmonary function, sleep disorder indices, and exacerbation frequency, suggesting its potential as an important indicator for early OVS identification and severity evaluation despite no significant difference in BMI.

**Keywords:** chronic obstructive pulmonary disease, obstructive sleep apnea, overlap syndrome, nutritional status, fat-free body mass index

## Introduction

Significant comorbidities are frequently linked to chronic obstructive pulmonary disease (COPD), which might further exacerbate the illness's clinical course and prognosis of the disease.<sup>1</sup> Overlap syndrome is gaining attention, where chronic conditions like Obstructive Sleep Apnea (OSA) and Chronic Obstructive Pulmonary Disorder (COPD) often co-occur and lead to adverse health consequences that may overlap in OVS,<sup>2</sup> Evidences have shown that patients with OVS experience exacerbated negative health effects and thus worse clinical outcomes than those with OSAS or COPD alone.<sup>3</sup> For several years, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) has consistently emphasized the importance of addressing the prevalence of sleep disorders in COPD patients and actively conducting early screening and

timely treatment.<sup>1</sup> Despite the well-documented adverse effects of overlap syndrome, its recognition and diagnosis remain suboptimal. Many patients with COPD may not be routinely screened for OSA or other comorbidities, leading to a delay in the identification of overlap syndrome.<sup>4</sup> This delay can result in missed opportunities for early intervention and appropriate management strategies that could potentially improve patient outcomes.

In the assessment of OVS, for COPD, spirometry is a frequently used method to measure parameters like FEV<sub>1</sub> and FEV<sub>1</sub>/FVC ratio. But it merely shows the extent of airway restriction and is unable to fully evaluate the combined condition's overall impact.<sup>5</sup> In terms of OSA, polysomnography (PSG) is the traditional and accurate way to determine AHI and oxygen desaturation index.<sup>6</sup> However, it is expensive and cumbersome because patients must spend the night in a sleep lab. The absence of an integrated assessment model is one significant flaw. The complicated relationships and synergistic effects of OSA and COPD are largely ignored by current approaches, which primarily assess the two conditions separately.

Body Mass Index (BMI) has historically been the main indicator of a person's nutritional condition, although it is inaccurate in reflecting the body's muscle mass and energy stores.<sup>7</sup> Recently, the Fat-Free Mass Index (FFMI) has emerged as a more precise tool for evaluating patient nutritional status. After accounting for stature and nutritional status among individuals with COPD, multiple investigations have determined that the fat-free mass index (FFMI) is strongly associated with respiratory muscle function and physical endurance.<sup>8</sup> Prior research has predominantly concentrated on the nutritional status of COPD or OSA patients individual,<sup>9,10</sup> with limited focus on the OVS population. To better understand the OVS population, improve prognostic evaluations, and develop tailored treatment plans, this study intends to examine the nutritional state of OVS patients and its relationships with a range of clinical markers.

## Materials and Methods

### Participants and Study Design

A total of 364 participants (203 with OVS and 161 pure COPD) were enrolled. Participants were recruiting from tertiary hospitals' respiratory and sleep medicine clinics over 60 months (September 2019 to September 2024). About OVS group, Inclusion Criteria were (1) Adults aged  $\geq 40$  years. (2) Confirmed diagnosis of COPD (post-bronchodilator FEV<sub>1</sub>/FVC  $< 0.7$ ) 1 and moderate-to-severe OSA (apnea-hypopnea index, AHI  $\geq 15$  events/hour).<sup>11</sup> (3) Stable clinical status (no acute exacerbations or hospitalization within the preceding 4 weeks). Exclusion criteria were (1) cardiovascular disease, (2) neuromuscular impairment, (3) psychiatric disease, or (4) osteoarticular disorders. The exclusion criteria for COPD were the same as for OVS. All patients are willing to participate and sign the informed consent. The study protocols were approved by the Ethics Committee of the First Affiliated Hospital of Soochow University ((No. 2017–017)) and all patients provided written informed consent. The study procedures were conducted in accordance with the principles outlined in the Declaration of Helsinki of the World Medical Association.

### Experimental Methods

Demographic characteristics such as BMI, smoking index, acute exacerbation in the last year, and co-morbidities were performed on all the included subjects. FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, AHI, L-SaO<sub>2</sub>, FFMI, and prevalence of malnutrition were further asked about the two groups. The Dyspnea Scale (mMRC), 6-minute walking test (6MWT) COPD symptom Severity score (CAT), and the Epworth Sleepiness Scale (ESS) were evaluated.

**Pulmonary function test:** The test was performed by Masterscreen-PFT of JAEGER Company in Germany according to ATS/ERS guidelines. Subjects completed three standard expiratory and inspiratory cycles, and the variation rate of each lung function parameter was  $< 5\%$ . The pulmonary function parameters including FEV<sub>1</sub>%pred, and FEV<sub>1</sub>/FVC were recorded after the bronchodilation test.

**Nocturnal polysomnography:** It was performed according to the standard instrumentation and procedures.<sup>11</sup> The patient's sleep is monitored using the FACumen Pro3000 polysomnograph produced by Caditex. Before the test, the subjects were instructed not to drink alcohol on the test day, not to drink stimulant drinks such as coffee, and to stop taking sedatives and sleeping pills 8 hours before the test. In the special sleep monitoring ward of the respiratory department of our hospital, the recording time was not less than 7 hours. The AHI and minimum blood oxygen saturation at night were noted.

Body composition analysis: Using the body composition analyzer (Tsinghua Tongfang BCA-2A). Its principle is direct segment multifrequency bioelectrical impedance measurement. The subjects were asked to wear light clothes, do no strenuous exercise 15 minutes before the test, and empty the bladder before the test, without a pacemaker, or heart stent, etc. We calculated FFMI by the following equation:

$FFMI = (FFM/height^2) (kg/m^2)$ . FFM was measured by bioelectrical impedance analysis.

## Statistical Methods

All data were statistically analyzed using SPSS 20.1 software. The measurement data conforming to the normal distribution were expressed as mean  $\pm$  standard deviation. The normality of the data was assessed using Kolmogorov–Smirnov tests. For normally distributed data, we used the independent-sample *t*-test or one-way analysis of variance (ANOVA). Categorical data were evaluated using a chi-squared test or Fisher’s exact test. Pearson’s or Spearman correlation coefficients were calculated to investigate potential relationships among the variables. A linear stepwise-regression model was employed to identify the variables contributing to the variation in FFMI in patients with stable COPD.  $P < 0.05$  was considered statistically significant.

## Results

### Characteristics of Study Participants

As presented in Table 1, patients in the OVS group had a significantly more acute AEs, proportion of co-morbidities and hospitalizations ( $P < 0.001$ ,  $P < 0.05$  and  $P < 0.001$ ) in the last year. No statistically significant differences were found between the two groups regarding gender, age, BMI and smoking index.

### Pulmonary Function and Sleep Apnea-Related Parameters

Table 2 showed that  $FEV_1\%$ pred,  $FEV_1/FVC$ , and 6MWT were all significantly lower in the OVS group compared with the COPD (all  $p < 0.05$ ), while AHI, L-SaO<sub>2</sub>, ESS, CAT, and MMRC were higher than the COPD. The OVS group shows lower FFMI and higher prevalence of malnutrition than the patients with COPD.

### Difference Between Lower FFMI and Normal FFMI Group in the OVS Group

The OVS group was divided into a low FFMI group and a normal FFMI group, with the cutoff value of FFMI being less than 17kg/m<sup>2</sup>. As shown in Table 3, patients with lower FFMI had lower  $FEV_1\%$ pred,  $FEV_1/FVC$ , L-SaO<sub>2</sub>, and 6MWT with  $p$  all  $< 0.5$ . Besides, AHI, MMRC, times of acute exacerbations and hospitalizations in the last year were higher (all  $p < 0.05$ ) in the lower FFMI group. There were no differences between BMI and CAT in the lower FFMI and normal FFMI OVS groups.

**Table 1** Comparison of Anthropometric Characteristics Between Patients with OVS and COPD

Variables	COPD Group N = 203	OVS Group N = 161	<i>p</i>
Males, n (%)	176(86.7)	134(83.2)	0.36
Age, yrs	61.69 $\pm$ 7.89	60.81 $\pm$ 7.76	0.29
Smoking index (package year)	387.43 $\pm$ 27.36	392.43 $\pm$ 24.54	0.07
BMI, kg/m <sup>2</sup>	23.56 $\pm$ 3.50	24.13 $\pm$ 2.26	0.06
AEs in the past year (frequency)	2.08 $\pm$ 1.3	2.68 $\pm$ 2.3	<0.001
Hospitalizations in the past year (frequency)	0.52 $\pm$ 1.12	1.34 $\pm$ 2.23	<0.001
Co-morbidities			
Hypertension, n (%)	37(18.23)	46(28.57)	0.02
Diabetes, n (%)	16(7.88)	26(16.15)	0.01
CHD, n (%)	9(4.43)	16(9.94)	0.04
PAH, n (%)	8(3.94)	15(9.32)	0.04

**Abbreviations:** BMI, body mass index; AEs in the past year, acute exacerbations in the past year; COPD, Chronic obstructive pulmonary disease; OVS, overlap syndrome; CHD, Coronary Heart Disease; PAH, Pulmonary Arterial Hypertension;

**Table 2** Prevalence of Pulmonary Function and Sleep Apnea-Related Parameters in Patients with OVS Compared with Patients with OSAS

Variables	COPD Group N = 203	OVS Group N = 161	p
AHI (time/h)	2.62 ± 1.80	25.81 ± 11.83	<0.001
L-SaO <sub>2</sub> (%)	87.8 ± 4.02	82.19 ± 7.04	<0.001
ESS scores (mean ± SD)	4.81 ± 2.25	11.16 ± 3.80	0.03
6MWT (m)	570.47 ± 68.20	550.1 ± 80.3	0.01
FEV <sub>1</sub> %pred	60.63 ± 23.18	55.12 ± 16.83	0.01
FEV <sub>1</sub> /FVC (%)	59.24 ± 12.39	56.35 ± 11.04	0.02
CAT scores (mean ± SD)	11.51 ± 5.70	13.17 ± 4.21	0.02
MMRC scores (mean ± SD)	1.32 ± 0.99	2.17 ± 1.05	0.04
FFMI (kg/m <sup>2</sup> )	17.30 ± 1.69	16.70 ± 1.23	<0.001
Prevalence of Malnutrition (%)	42.36%	54.04%	0.03

**Abbreviations:** AHI, Apnea–hypopnea index; L-SaO<sub>2</sub>, Lowest oxygen desaturation; ESS Epworth sleepiness scale score, FEV<sub>1</sub>, forced expiratory volume in 1s of predicated; FVC, forced vital capacity; MMRC, Modified British Medical Research Council; CAT, COPD assessment test; FFMI, fat free mass index; 6MWT, 6 minutes walking test.

**Table 3** Comparison of Lung Function and Sleep Indexes of OVS Patients in Low FFMI Group and Normal FFMI Group

Variables	Low FFMI N = 85	Normal FFMI N = 76	p
BMI (kg/m <sup>2</sup> )	24.49 ± 2.27	25.05 ± 1.66	0.07
CAT	13.21 ± 4.01	12.77 ± 4.32	0.60
MMRC	2.54 ± 1.01	2.10 ± 0.88	0.04
6MWT (m)	545.47 ± 55.20	586.76 ± 74.20	0.04
ESS (score)	15.50 ± 2.45	13.71 ± 3.01	0.03
AHI (time/h)	37.97 ± 11.08	29.44 ± 13.89	<0.001
L-SaO <sub>2</sub> (%)	79.93 ± 5.82	88.45 ± 7.72	<0.001
FEV <sub>1</sub> %pred (%)	48.15 ± 15.31	67.05 ± 14.22	<0.001
FEV <sub>1</sub> /FVC (%)	36.37 ± 9.70	47.73 ± 9.86	<0.001
AEs in the past year (frequency)	2.38 ± 1.30	1.78 ± 2.30	0.04
Hospitalization in the past year (frequency)	1.56 ± 1.12	1.13 ± 2.25	0.03

**Abbreviations:** BMI, body mass index; AHI, Apnea–hypopnea index; L-SaO<sub>2</sub>, Lowest oxygen desaturation; ESS Epworth sleepiness scale score, FEV<sub>1</sub>, forced expiratory volume in 1s of predicated; FVC, forced vital capacity; MMRC, Modified British Medical Research Council; CAT, COPD assessment test; FFMI, fat free mass index; AEs in the past year, acute exacerbations in the past year;

## Correlation Between FFMI and Various Indicators in the OVS Group

Correlation analysis showed that in OVS group, FFMI was positively correlated with FEV<sub>1</sub>%pred and FEV<sub>1</sub>/FVC ( $p < 0.05$ ). Additionally, FFMI was negatively correlated with AHI, MMRC, times of acute exacerbations and hospitalizations in the last year,  $p$  all  $< 0.05$ . There was no significant correlation with 6MWT and ESS. Detailed results were presented in [Table 4](#).

## Multiple Regression Analysis Between FFMI and Lung Function and Sleep-Related Measures

In a regression analysis where FFMI was designated as the dependent variable and AHI, L-SaO<sub>2</sub>, FEV<sub>1</sub>%pred, and FEV<sub>1</sub>/FVC were considered as independent variables, a significant positive correlation was observed between FFMI and FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, and L-SaO<sub>2</sub>. The standardized regression coefficients indicated these relationships with respective  $p$ -values of 0.031, 0.043, and 0.029. Conversely, AHI exhibited a negative correlation with FFMI. The statistical significance of these  $p$ -values was further highlighted, with  $p = 0.031$ , as detailed in [Table 5](#).

**Table 4** Correlation Analysis Between FFMI Level and Pulmonary Function and Sleep Indicators in the OVS Group

Variables	FFMI	
	r	p
6MWT (m)	0.25	0.12
AHI (time/h)	-0.32	<0.01
L-SaO <sub>2</sub> (%)	0.23	0.01
FEV <sub>1</sub> %pred (%)	0.27	<0.01
FEV <sub>1</sub> /FVC (%)	0.23	<0.01
MMRC	-0.23	0.02
ESS	-0.24	0.06
AEs in the past year (frequency)	-0.15	0.03
Hospitalization in the past year (frequency)	-0.25	0.04

**Abbreviations:** AHI, Apnea-hypopnea index; L-SaO<sub>2</sub>, Lowest oxygen desaturation; ESS Epworth sleepiness scale score, FEV<sub>1</sub>, forced expiratory volume in 1s of predicated; FVC, forced vital capacity; MMRC, Modified British Medical Research Council; CAT, COPD assessment test; FFMI, fat free mass index; 6MWT, 6 minutes walking test;

**Table 5** Multiple Linear Regression Analysis with FFMI as the Dependent Variable

Variables	β	SE	p
AHI (time/h)	-0.29	0.043	0.031
L-SaO <sub>2</sub> (%)	0.36	0.041	0.029
FEV <sub>1</sub> %pred (%)	0.16	0.031	0.031
FEV <sub>1</sub> /FVC (%)	0.17	0.032	0.043

**Abbreviations:** AHI, Apnea-hypopnea index; L-SaO<sub>2</sub>, Lowest oxygen desaturation; FEV<sub>1</sub>, forced expiratory volume in 1s of predicated; FVC, forced vital capacity;

## Discussion

The findings revealed a higher prevalence of malnutrition in OVS patients compared to those with COPD alone. OVS patients with combined malnutrition also exhibited lower levels of FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, and L-SaO<sub>2</sub>, as well as higher AHI, CAT, ESS, and MMRC scores, along with more acute exacerbations and hospitalizations in the previous year compared to COPD patients. In the OVS group, although BMI did not show statistically significant abnormalities, FFMI was positively associated with FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, and L-SaO<sub>2</sub>, while negatively correlated with AHI, acute exacerbations, and hospitalizations in the last year. These results highlight the importance of evaluating FFMI in OVS patients for the development and implementation of effective treatment and follow-up plans.

Compared to patients with single COPD, those with OVS have worse lung function (lower FEV<sub>1</sub> and FEV<sub>1</sub>/FVC), higher symptom scores (CAT and MMRC), and more acute exacerbations and hospitalizations. OVS is a complicated condition more than the simple mix of COPD and OSA.<sup>4,12,13</sup> The combination of OSA-related apnea/hypopnea and COPD-induced airway and parenchymal damage significantly reduces lung ventilation and gas exchange.<sup>5</sup> Wheezing and dyspnea symptoms worsen, and sleep apnea interferes with sleep, resulting in daily sluggishness and a lower quality of life.<sup>14</sup> Weakened immunity and cardiac reserve from OSA increase the likelihood of acute exacerbation and hospitalization.<sup>5,14,15</sup>

In recent years, with the development of bioelectrical impedance to determine the specific composition of the human body, several studies<sup>16–18</sup> had indicated that the body fat mass and was more sensitive to predicting OSA and COPD than BMI. Slinde et al confirmed that FFMI can independently predict the risk of death in COPD.<sup>8</sup> Therefore, this study used FFMI to evaluate the clinical features and muscle status of OVS patients. We defined FFMI < 17 kg/m<sup>2</sup> as malnutrition according to the recommendations of the European Society for Clinical Nutrition and Metabolism (ESPEN), and the results showed a very high incidence of malnutrition within the OVS group. COPD increases energy consumption and impairs digestion, and OSA disrupts metabolism and endocrine function, which contributes to the occurrence of malnutrition.<sup>5</sup> Therefore, OVS presents a more challenging clinical scenario with multi-faceted impacts on patients' health and well-being.<sup>2,5,19</sup>

The OVS group was categorized into low FFMI and normal FFMI subgroups. The research revealed that the AHI in the low FFMI subgroup was lower compared to the normal FFMI subgroup. Further correlation analysis indicated a negative relationship between FFMI values and AHI, suggesting that lower FFMI may mitigate the occurrence of apnea events to some extent among OVS patients. Additionally, FFMI values were positively associated with FEV1% pred and FEV1/FVC, implying a close link between low FFMI and the severity of COPD, which aligns with findings from the ALEC study<sup>20</sup> and Bianco et al.<sup>21</sup> The possible reasons can be summarized as follows: Firstly, a low FFMI typically reflects a decrease in fat-free mass, including muscle mass. In OVS patients, respiratory muscle strength is crucial for maintaining normal lung function and sleep breathing patterns. A lower FFMI suggests compromised strength of respiratory muscles, such as the diaphragm and intercostal muscles. For COPD patients, inadequate respiratory muscle strength can lead to restrictions in both expiratory and inspiratory functions,<sup>22</sup> resulting in decreased pulmonary ventilation capacity and poor lung function.<sup>23,24</sup> However, the upper airway muscles' support during sleep is essential for preserving airway patency in patients with OSA.<sup>25</sup> The muscles of the upper airways, such as the neck and pharynx, may also be weak when FFMI is low, which makes them more likely to relax and collapse as you sleep. This makes airway blockage worse and results in more severe sleep apnea episodes.<sup>26</sup> Additionally, a lower FFMI may be linked to a decreased metabolic rate; disturbances in metabolic regulation may have an indirect impact on the central control systems that regulate breathing while you sleep, which could exacerbate apneic episodes.<sup>27</sup> Furthermore, OSA may exacerbate the inflammatory condition that is already present in COPD, which is classified as a chronic inflammatory illness.<sup>28</sup> Malnutrition is common in patients with lower FFMI, which can lead to weakened immune systems and protracted inflammatory reactions. It has been demonstrated that inflammatory mediators affect the shape of lung tissue as well as airway function, which results in a decline in pulmonary function.<sup>29</sup> Finally, inflammation may exacerbate the severity of hypoxia-reperfusion injury that occurs during obstructive sleep apnea episodes.<sup>30,31</sup>

In conclusion, FFMI is a more objective nutritional assessment index for the complicated patient group of OVS since it removes the influence of body fat on body weight, in contrast to BMI. The prognosis improvement in OVS patients is significantly correlated with FFMI. A greater FFMI may improve lung function and reduce sleep apnea symptoms, which could improve patient outcomes. In clinical practice, tracking a patient's FFMI level is crucial for assessing their nutritional status and prognosis. Patients' prognosis may be improved by raising their FFMI level through nutritional interventions. The existing sleep breathing markers, such as AHI and L-SaO<sub>2</sub> during the night, may not accurately reflect the sporadic and ongoing hypoxia experienced by OVS patients, which is one of the study's weaknesses. To further investigate its effect on the prognosis of OVS patients, future research should think about incorporating additional markers, such as the percentage of hypoxia and the length of time blood oxygen saturation falls below 90%.

## Disclosure

The authors report no conflicts of interest in this work.

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