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REVIEW

The Association Between COPD, Acute Exacerbations of COPD, and Survival in COPD, with Fat-Free Body Mass Index: A Systematic Review and Meta-Analysis

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Objective: Nutritional status critically influences disease progression and prognosis in chronic obstructive pulmonary disease (COPD). This meta-analysis evaluates the clinical significance of fat-free mass index (FFMI) in COPD prognosis.

Methods: A systematic search of PubMed, Embase, Web of Science, Scopus, Ovid, and Cochrane Library (up to December 7, 2024) identified studies comparing FFMI among non-smokers, smokers, COPD patients, and those with acute exacerbations (AE) or mortality. Pooled weighted mean differences (WMD), odds ratios (OR), and hazard ratios (HR) were calculated. Subgroup analyses assessed smoking status and AE sources, with Sensitivity analyses, Egger's test and trim-and-fill method evaluating robustness and publication bias.

Results: A pooled analysis including 17 studies involving 4239 patients with COPD revealed that FFMI levels in COPD group were significantly lower than those in control group (WMD = −0.84; 95% CI: −1.63, −0.05). Among COPD patients, no significant difference in FFMI levels was found between AE and non-AE groups (WMD = −1.32; 95% CI: −2.76, 0.11); furthermore, FFMI levels in death group were significantly lower compared to those in survival group (WMD = −1.23; 95% CI: −1.73, −0.74). Notably, FFMI emerged as a critical factor associated with AE occurrence (OR = 0.82; 95% CI: 0.72, 0.95) and survival outcomes (HR = 0.89; 95% CI: 0.86, 0.93) among patients with COPD.

Conclusion: Low FFMI is strongly associated with adverse disease progression and poor prognosis in COPD. Tailored interventions targeting nutritional status and body composition may optimize disease management and survival outcomes.

Keywords: chronic obstructive pulmonary disease, fat-free body mass index, body composition, prognosis, acute exacerbation, mortality

Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition characterized by progressive and worsening airflow limitation. The primary manifestations of this disease include chronic respiratory symptoms such as cough, sputum production, and dyspnea. Studies have presented that the global prevalence of COPD among patients is approximately 10.3%, with an all-cause mortality rate of 4.72%.[1,2] Furthermore, COPD ranks among the top three causes of death worldwide, placing patients at significant risk for severe disease burden and poor prognosis.[3] Consequently, identifying factors associated with poor prognosis in COPD patients is crucial for facilitating early intervention and enhancing survival rates.

Nutritional status is closely related to the occurrence, progression, and outcome of diseases. Malnutrition is an important factor contributing to poor prognosis in COPD, with a prevalence rate of 30% for COPD patients who also

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experience malnutrition.[4] Body mass index (BMI) and fat-free mass index (FFMI) are widely utilized for assessing nutritional status. While BMI plays a crucial role in evaluating the risk of COPD and its associated poor prognosis,[5,6] it presents challenges in distinguishing the ratio between body fat and muscle mass. Consequently, determining the specific impact of body composition on COPD through BMI becomes increasingly difficult.

FFMI calculated as fat-free mass (kg) divided by height squared (m^2), is a validated measure of lean body mass.[7] Unlike BMI, FFMI distinguishes individual muscle mass from adipose tissue, making it a critical indicator for evaluating sarcopenia and nutritional status in chronic diseases such as COPD. It is important to note that low FFMI is commonly observed among patients with COPD who show normal BMI.[8] Research on COPD has demonstrated that individuals with low FFMI exhibit characteristics such as reduced exercise capacity, diminished lung function, and decreased muscle strength.[9,10] These findings suggest that FFMI may serve as a significant indicator for assessing the prognosis of patients with COPD. Identifying FFMI as a prognostic marker could support early nutritional interventions, potentially improving outcomes in COPD patients. However, the relationship between FFMI and COPD remains controversial due to insufficient pooled evidence.[11,12]

Therefore, we employed a quantitative and qualitative pooled analysis to elucidate the significance of FFMI in the poor prognosis associated with COPD.

Materials and Methods

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered with INPLASY (http://INPLASY.com). (registration number: INPLASY202520070).

Search Strategy

We conducted a systematic and comprehensive literature search for publications prior to December 7, 2024 in PubMed, Embase, Web of Science, Scopus, Ovid, and Cochrane Library databases. The search primarily included—though was not limited to—the following terms: "chronic obstructive pulmonary disease", "COPD", "fat free mass index", "FFMI", "mortality", "exacerbation", "progression" "poor prognosis" (Supplementary Table 1 for detailed information on the search strategy and corresponding databases).

Eligibility Criteria

Inclusion criteria were as follows: (1) Prospective or retrospective study; (2) Diagnosis of COPD was based on the global initiative for chronic obstructive lung disease report; (3) The literature should encompass the target population or outcome events of our study; (4) Quantitative data regarding FFMI (mean ± standard deviation [SD]) should be obtainable or convertible through algorithm;[13,14] (5) Statistical results derived from univariate Cox proportional hazard model and univariate logistic regression model.

Exclusion criteria were as follows: (1) case report, review, meta-analysis, comment, letter, conference abstract and animal or cell study; (2) Data that could not be extracted or converted by algorithm.

FFMI Measurement, Study Definition and Outcome Event

FFMI was obtained using bioelectrical impedance analysis, with the results presented as mean ± SD. The acute exacerbation (AE) is defined as a sudden worsening of respiratory symptoms—including cough, phlegm production, wheezing, and difficulty breathing—that necessitates additional treatment or hospitalization. The non-smoking (non-SC) group was characterized by the absence of any previous smoking history. Conversely, the smoking (SC) group was defined as current smokers or ex-smokers. Outcome events included AE and mortality in patients with COPD. Furthermore, we conducted an analysis to compare FFMI differences between non-SC, SC and COPD groups.

Quality Assessment (Risk of Bias) and Data Extraction

The two authors (BS, XL) independently reviewed the abstracts and full texts of studies that met the inclusion criteria. Another two author (LS, ML) employed the Newcastle-Ottawa Quality Assessment Scale (NOS) to evaluate the quality of the literature.[15] NOS is a widely utilized tool for assessing quality in case-control and cohort studies. It evaluates the

quality of included studies through three modules with a total of eight items, specifically addressing population selection, comparability, and exposure/outcome. The total score of NOS is 9 "stars", with higher scores indicating superior quality of included studies. Specifically, scores ranging from 7 to 9 "stars" denote high-quality studies, scores between 4 and 6 "stars" indicate moderate quality, while scores from 0 to 3 "stars" reflect low-quality studies.

The extracted data encompassed the following variables: first author's name, publication date, country, study type, comparison group, age, gender, smoking history, BMI, forced expiratory volume in the first second as a percentage of expected value (FEV_1%), forced expiratory volume in the first second/forced vital capacity ratio (FEV_1/FVC), sample size, FFMI or obtained by algorithm (mean ± SD),[13,14] odds ratios (OR), hazard ratios (HR), and respective 95% confidence intervals (CI) for both OR and HR. In the event of any disputes arising during this process, a discussion may be held with an arbitrator (XH).

Data Synthesis

The clinical significance of FFMI in COPD was evaluated by pooled weighted mean difference (WMD), OR, and HR along with their corresponding 95% CI. Cochran's Q statistic and inconsistency value (I^2) were employed to assess the heterogeneity among the included studies. If $p< 0.05$ or $I^2 \geq 50\%$, it indicated significant heterogeneity, prompting the use of a random-effect model and the DerSimonian-Laird (DL) method for analysis. Conversely, when no significant heterogeneity was present, a fixed-effect model and inverse-variance (IV) method were utilized. For dichotomous outcomes, OR and HR were converted to log-OR and log-HR using the logit transformation respectively. Corresponding standard errors were derived from 95% confidence intervals. Transformed effects were pooled via inverse-variance weighted meta-analysis on the log scale. Final estimates were back-transformed and reported with 95% CIs.

Based on the smoking status of the control group, participants were categorized into non-SC group and SC group. Additionally, COPD patients experiencing AE according to their source were classified as either outpatients or inpatients for subsequent subgroup analyses. In subgroup analysis, for continuous variables(FFMI) inverse variance weighted meta-analysis was used on the scale of measurement using the DerSimonian-Laird estimator for tau-squared and the calculation of I-squared, based on Q, the heterogeneity statistic. Meta-regression will be performed if ≥10 studies contribute to a comparison with substantial heterogeneity. The sensitivity analysis was performed by sequentially excluding one study at a time and recalculating the effect size (one-by-one elimination method). If excluding any specific literature did not significantly affect the results, this suggested that our findings were stable and reliable. Publication bias was judged through Egger's test as well as funnel plots utilizing a trim-and-fill method. The meta-analysis was conducted using the meta package in Stata 16.0 software; a p-value of less than 0.05 was considered statistically significant.

Results

Study Selection and Characteristics

We conducted a comprehensive literature search across several databases, including PubMed (n=632), Embase (n=268), Web of Science (n=229), Scopus (n=77), Ovid (n=78), and Cochrane Library (n=105). In total, 1389 studies were initially identified. After removing 490 duplicate records, we reviewed 899 studies based on the titles and abstracts. Following this review, we excluded 12 case reports/letters, 88 conference abstracts, 115 reviews or meta-analyses, and 19 studies focused on animal or cell research. Consequently, the full texts of the remaining 665 articles were reviewed; among them, 203 studies were unrelated to COPD, 310 studies were irrelevant to FFMI, 105 studies did not address the outcome events relevant to our investigation, and original data from 29 studies could not be extracted. Ultimately, 17 studies involving a cohort of 4239 patients with COPD were pooled and reviewed in strict accordance with the PRISMA guidelines (Figure 1).

All studies originated from various countries, including Brazil (n=4), Greece (n=2), France (n=2), China (n=2), Japan (n=1), Britain (n=1), Italy (n=1), Germany (n=1), Sweden (n=1), and Netherland (n=1), with one study from a multi-center international investigation. Five studies examined the differences in FFMI between patients with COPD and

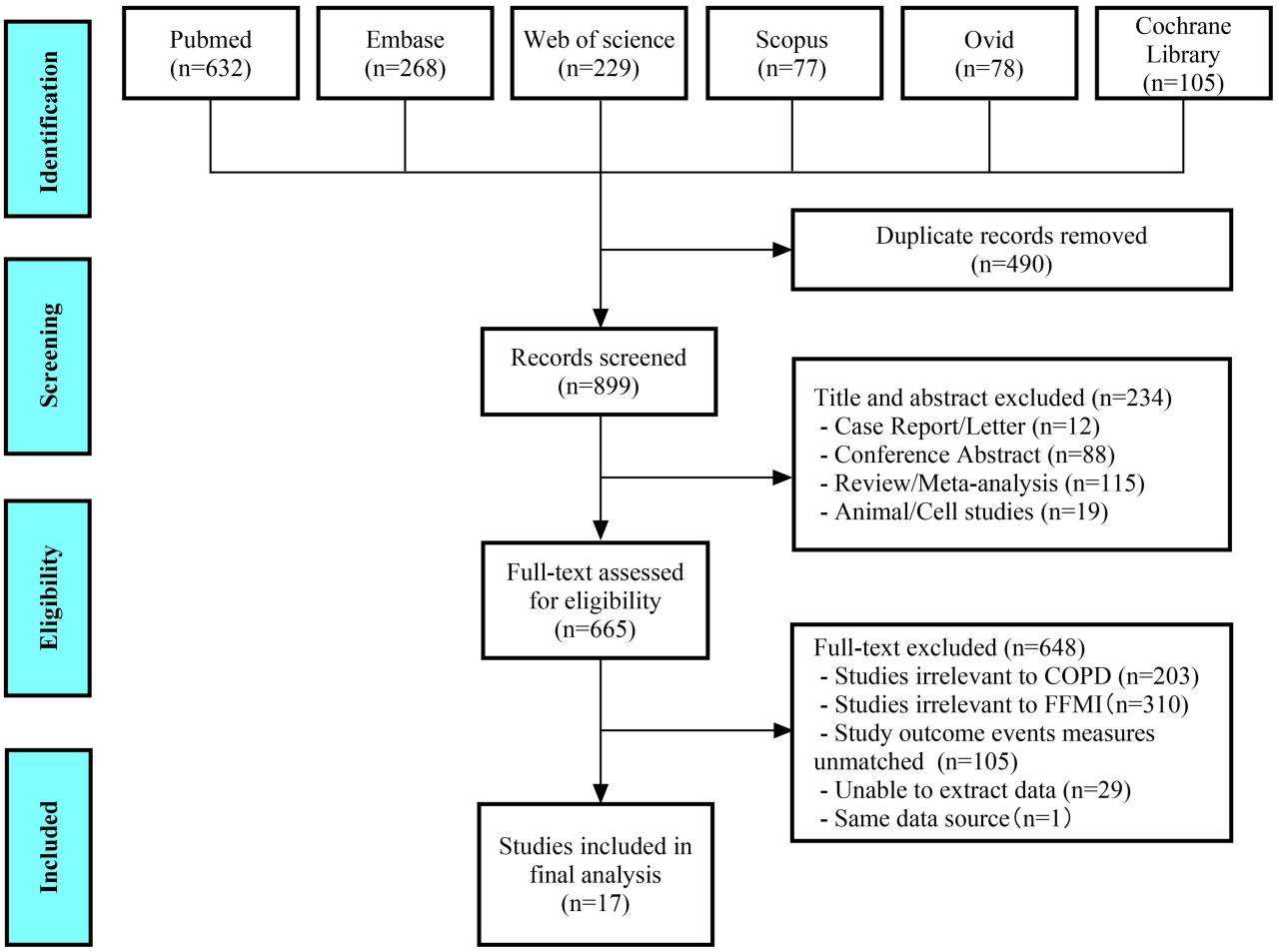

Figure 1 Diagram of the preferred reporting items for systematic review and meta-analysis (PRISMA).

control groups; among these, two studies reported WMD between COPD and non-SC groups,[16,17] while four studies focused on WMD between COPD and SC groups.[17–20] Furthermore, four studies investigated the relationship between FFMI and AE in patients with COPD; three of these studies summarized WMD for AE versus non-AE cases,[21–23] whereas four studies displayed OR associated with AE.[21,22,24] Eight studies analyzed the association between FFMI and mortality among patients with COPD; six of these studies performed pooled WMD analyses concerning survival versus death outcomes,[11,12,25–28] while another six conducted HR analyses related to mortality.[11,12,26,27,29,30] Detailed information regarding each included study (Supplementary Tables 2–4) indicated that a total of 16 studies were classified as high quality, while two studies were considered medium quality following NOS scoring criteria. The primary reasons for this classification included: (1) inability to ascertain inter-group comparability or imbalances therein; (2) no response rate or missing data rate (Supplementary Table 5).

The Difference in FFMI Between COPD and Control Groups

The results indicated significant heterogeneity among the included studies regarding FFMI differences between COPD and control groups (I^2 = 84.3%, P < 0.001). A random-effect model was employed for analysis. The findings revealed that FFMI levels in COPD group were significantly lower than those in control group (WMD = −0.84, 95% CI: −1.63, −0.05, P = 0.038). Based on the subtypes of control group, participants were categorized into non-SC and SC groups. Heterogeneity tests showed no significant heterogeneity within all relevant studies for both non-SC group (I^2 = 0.0%, P = 0.331) and SC group (I^2 = 8.2%, P = 0.337), suggesting that smoking status may be a potential source of heterogeneity. The pooled results from the subgroup analysis demonstrated that FFMI levels were significantly lower in COPD group

compared to those in non-SC group (WMD =−1.70, 95% CI: −2.30, −1.10, $P < 0.001$); however, there was no significant difference in FFMI between COPD and SC groups (WMD =−0.13, 95% CI: −0.39, 0.13, $P = 0.345$) (Figure 2).

Pooled Analysis of the FFMI Significance for AE Occurrences in Patients with COPD

There was significant heterogeneity ($I^2 = 90.6\%$, $P < 0.001$) among the included studies on FFMI between AE and non-AE groups in patients with COPD. Consequently, a random-effect model was utilized for analysis. The results revealed no statistically significant difference in FFMI levels between AE and non-AE groups among patients with COPD (WMD = −1.32, 95% CI: −2.76, 0.11, $P = 0.070$). Based on different sources, patients with COPD were categorized into outpatient and inpatient subgroups. The heterogeneity results demonstrated no significant heterogeneity across all relevant studies within the outpatient group ($I^2 = 0.0\%$, $P = 1.000$), revealing that patient origin may be a potential factor contributing to the heterogeneity. The pooled results from subgroup analyses indicated that among patients with COPD, FFMI levels were significantly lower in those experiencing AE compared to non-AE in both outpatient group (WMD =−0.40, 95% CI: −0.79, −0.01, $P = 0.047$) and inpatient group (WMD =−3.60, 95% CI: −4.90, −2.30, $P < 0.001$) (Figure 3). Furthermore, the heterogeneity results showed no significant variability in pooled OR related to FFMI for AE among COPD patients ($I^2 = 0.0\%$, $P = 0.439$), thereby utilizing a fixed-effect model. The outcomes suggested that FFMI was an associated factor influencing AE occurrences in COPD patients (OR = 0.82, 95% CI: 0.72, 0.95, $P = 0.007$) (Figure 4).

Pooled Analysis of the FFMI Significance for Assessing Survival in Patients with COPD

No significant heterogeneity was observed in pooled FFMI regarding the differences between death and survival outcomes in patients with COPD ($I^2 = 0.0\%$, $P = 0.636$). Consequently, a fixed-effect model was used for further

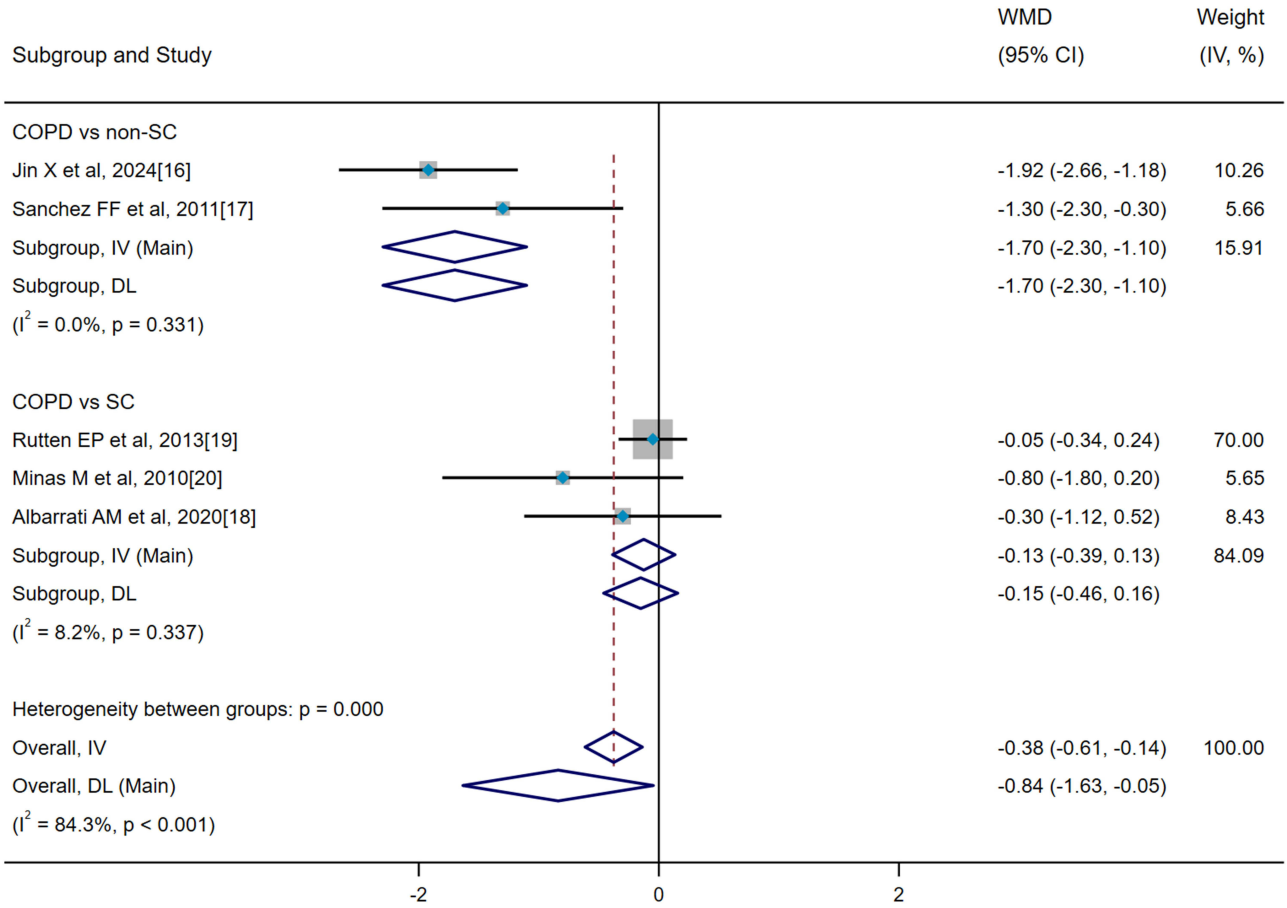

Figure 2 Pooled analysis of WMD (95% CI) for FFMI levels between COPD and control groups (non-SC and SC).

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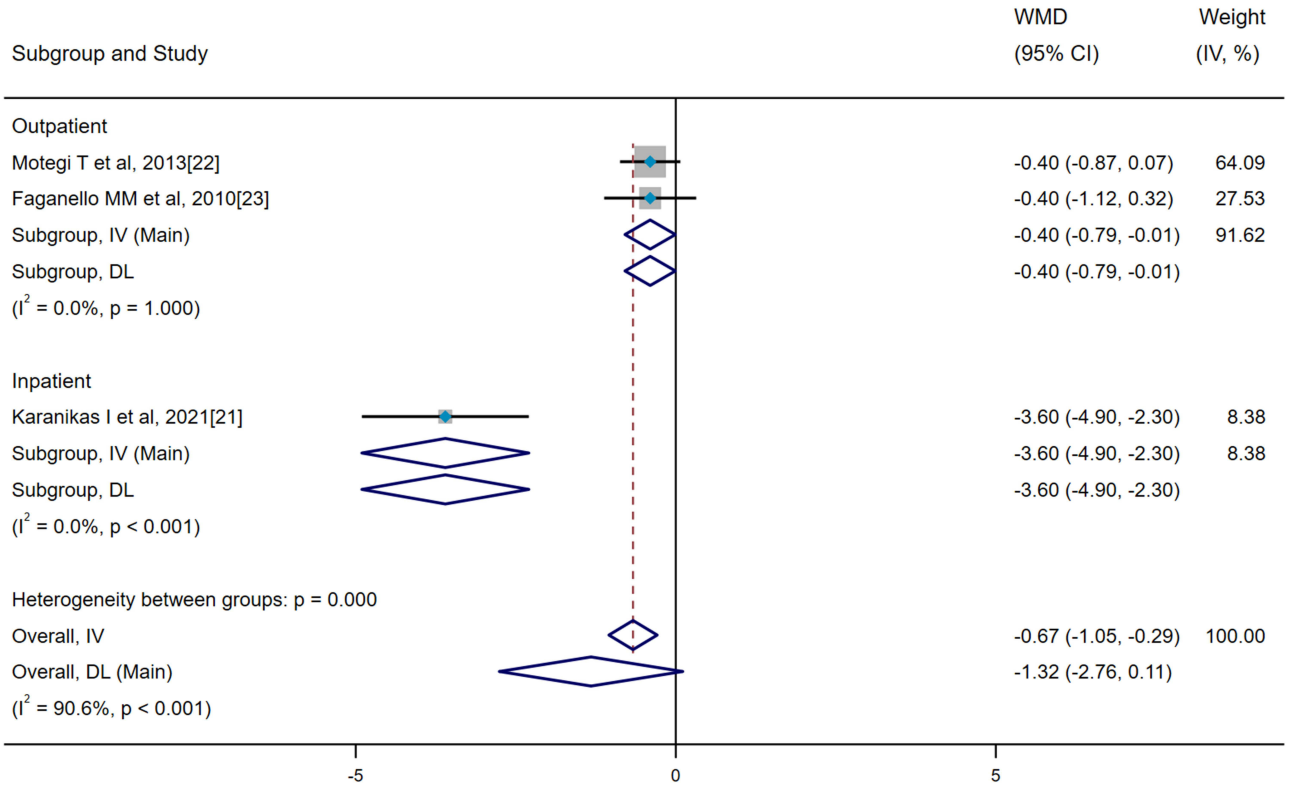

Figure 3 Pooled analysis of WMD (95% CI) for FFMI levels between AE and non-AE among patients with COPD (outpatient and inpatient subgroups).

analysis. The results revealed that FFMI levels among COPD patients in death group were significantly lower than those in survival group, demonstrating statistical significance (WMD = −1.23, 95% CI: −1.73, −0.74, $P < 0.001$) (Figure 5).

Similarly, heterogeneity results showed no significant variability among the studies on pooled FFMI related to HR for survival in COPD patients ($I^2 = 0.0\%$, $P = 0.694$). Using a fixed-effect model, the results indicated that FFMI served as a risk factor for survival among individuals with COPD (HR = 0.89, 95% CI: 0.86, 0.93, $P < 0.001$) (Figure 6).

Sensitivity Analysis and Publication Bias

Sensitivity analysis indicated that our findings were stable (Supplementary Figures 1–5). There was no supplementary literature by the trim-and-fill method, and the funnel plot results demonstrated a fundamental symmetry (Figure 7A–E).

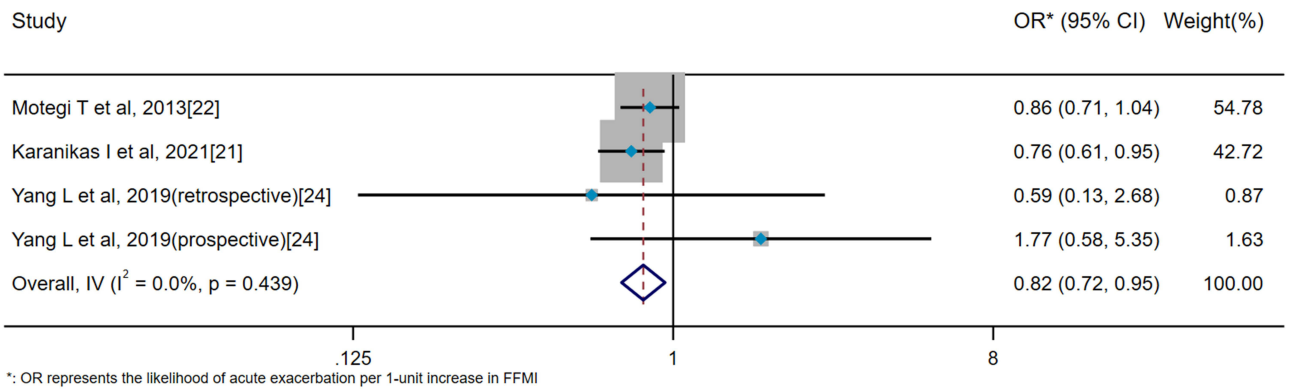

Figure 4 Pooled analysis of OR (95% CI) for FFMI and AE occurrences in patients with COPD.

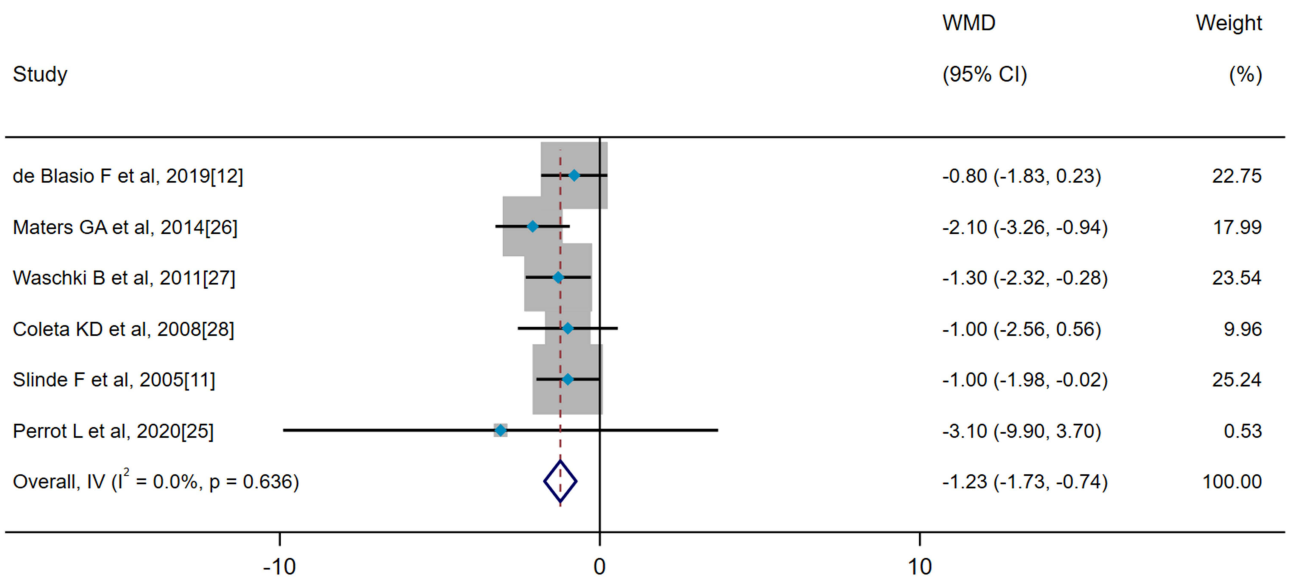

Figure 5 Pooled analysis of WMD (95% CI) for FFMI levels between death and survival among patients with COPD.

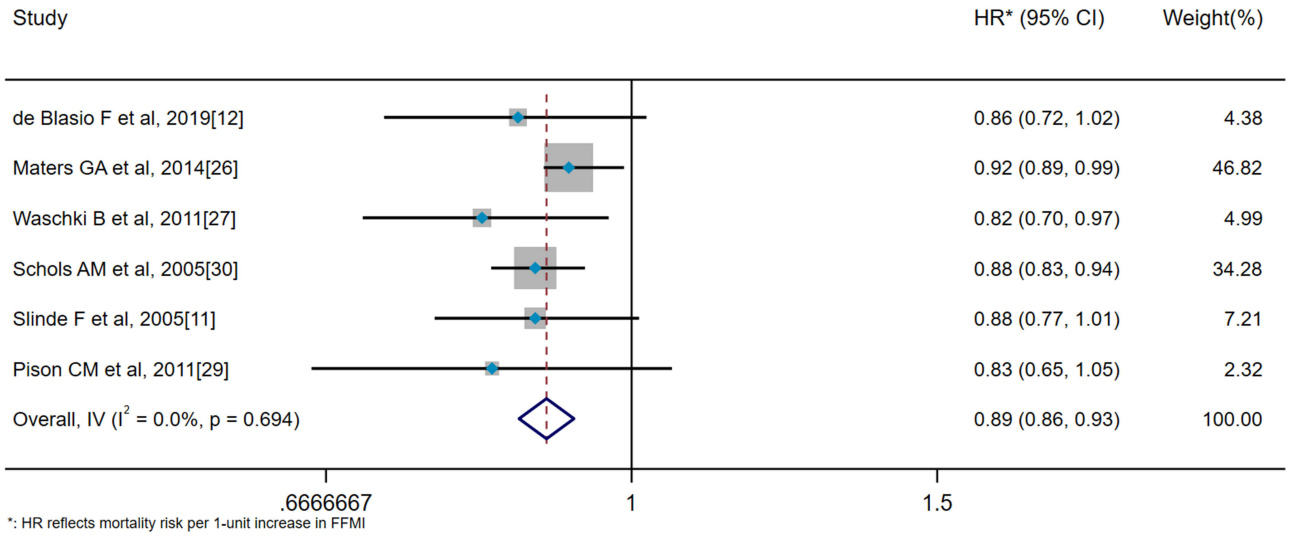

Figure 6 Pooled analysis of HR (95% CI) for FFMI and survival in patients with COPD.

Additionally, the outcomes of Egger's test suggested that there was no publication bias present in the results across each group in our study (Table 1).

Discussion

The relationship between nutritional status, body composition, and COPD has garnered widespread attention. However, there is a lack of pooled data regarding the effect of body composition on COPD. FFMI plays as an important indicator for assessing muscle and fat within body composition. Its utility in evaluating disease status and predicting poor prognosis in COPD remains disputable.[31] This study provides novel evidence that low FFMI levels are strongly associated with advanced disease severity and poor prognosis in COPD. Our findings align with the 2025 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report, which identifies malnutrition as a critical extrapulmonary manifestation of COPD.[32] While GOLD underscores the clinical significance of nutritional deficits, it lacks specific screening recommendations for muscle-specific impairments. Here, we propose fat-free mass index (FFMI) can serve as

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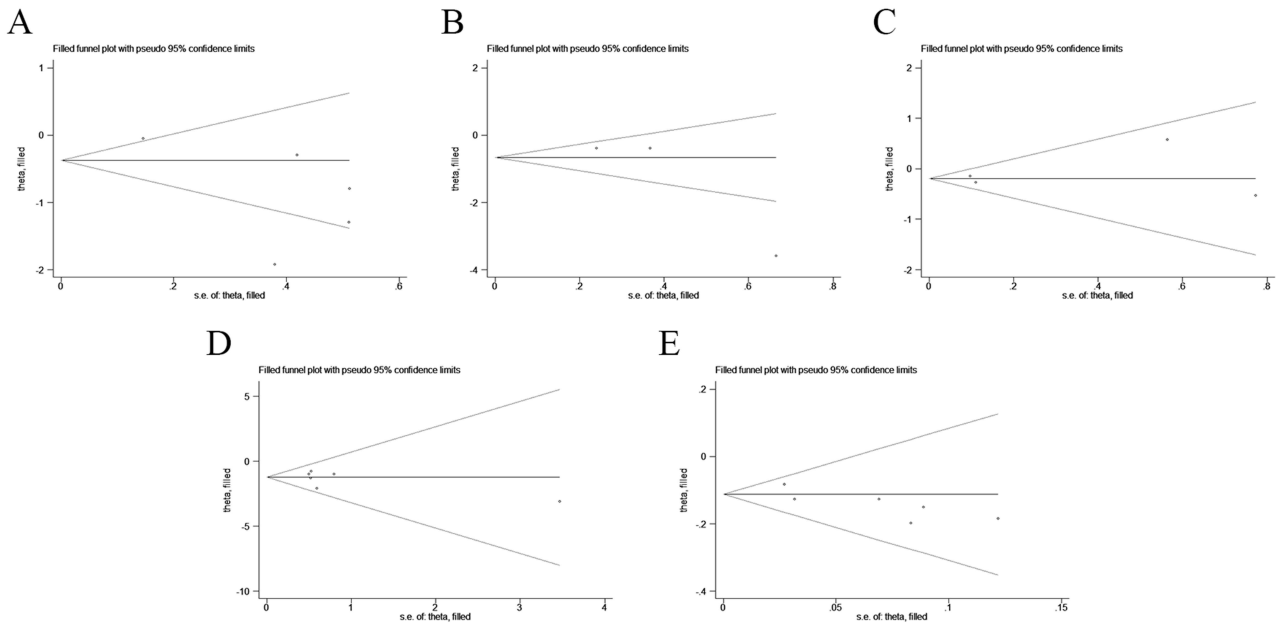

Figure 7 Funnel plots of the five groups included in pooled analyses (A: COPD vs Control; (**B**) Non-AE vs AE; C:AE(OR); (**D**) Survival vs Death; (**E**) Mortality (HR)).

a potential complementary biomarker to address this gap. Notably, our results demonstrate that FFMI effectively identifies muscle-related deficits in COPD patients—particularly those with preserved BMI but low muscle mass—a high-risk subgroup consistently overlooked in current guidelines.

Our results indicated that FFMI levels were significantly lower in COPD group compared to non-SC group. Given that FFMI is not influenced by fat mass, it reflects a disruption in the balance between muscle synthesis and catabolism in patients with COPD. On one hand, as the disease progresses, there is a noted decrease in nutrient intake among these patients.[5] On the other hand, an increase in energy metabolic expenditure has been observed,[6] which may play a crucial role in the reduction of FFMI levels among COPD patients. Furthermore, we found that while FFMI levels were lower in COPD group than in SC group, this difference did not reach statistical significance. Previous studies have indicated that airflow limitation could be a potential predictor of muscle atrophy in both COPD patients and smokers.[33] Concurrently, individuals with low muscle mass tend to exhibit higher smoking rates, reduced FFMI values, and an elevated risk of

Table 1 Egger's Test, Metatrim Filled Study and Publication Bias of Included Studies with Different Groups

Group	Included Items	Egger's Test		Metatrim Filled Study	Publication Bias
		t	P		
COPD vs Control (non-SC + SC, WMD)	6	−2.16	0.097	0	No
Non-AE vs AE (Outpatient + Inpatient, WMD)	3	−1.93	0.304	0	No
AE (Univariable, OR)	4	0.51	0.661	0	No
Survival vs Death (WMD)	6	−0.68	0.531	0	No
Mortality (Univariable, HR)	6	−2.45	0.071	0	No

Abbreviations: COPD, chronic obstructive pulmonary disease; SC, Smoking control; WMD, weighted mean difference; AE, acute exacerbation; OR, odds ratio; HR,: hazard ratio.

developing COPD.[34] The relationship between smoking and COPD is well-established; notably, long-term smoking has been shown to induce muscle atrophy in COPD rats, while also increasing inflammation and the expression of factors responsible for muscle protein degradation.[35] These findings imply that both smoking and worsening lung function may contribute to abnormalities in muscle metabolism among patients with COPD. Subgroup analyses stratified by smoking status and patient demographics aligned with the heterogeneity patterns observed in the ECLIPSE cohort, where COPD patients exhibited decreased FFMI levels in parallel with declining lung function.[36] Consistent with this, the COPDGene study revealed distinct body composition phenotypes associated with differential mortality risks, corroborating the clinical value of FFMI-based stratification in COPD prognostication.[37] Since the nutritional status of COPD may be influenced by various multifactorial elements such as diet, comorbidities, medications, and activity capacity, the mechanism underlying declines in FFMI among these patients remains unclear.

We further examined the prognostic significance of FFMI for adverse outcomes in COPD. The pooled results indicated that COPD patients experiencing AE had lower FFMI levels compared to those with non-AE; however, this difference was not statistically significant, potentially due to the limited number of included studies. Pooled analyses demonstrated a significant association between low FFMI and increased acute exacerbation risk in COPD patients. Previous research demonstrated that low FFMI levels were predictive of severe airflow limitation and emphysema in COPD patients,[38,39] which heightened the risk of AE. Additionally, reduced FFMI levels reflect diminished skeletal muscle mass among COPD patients,[40] leading to deteriorating lung function and an increased risk of AE.[41] Although low FFMI is a characteristic of malnutrition in patients with COPD, it does not correlate with airway inflammation or microbial colonization by pathogens;[42] furthermore, enhancing nutritional status does not appear to mitigate pneumonia risk.[43] Consequently, there is insufficient evidence supporting the involvement of low FFMI in AECOPD through infectious inflammatory pathways. Future studies should continue exploring the roles of nutritional status and muscle mass in AECOPD. Our pooled analysis revealed that FFMI levels among COPD patients were significantly lower in death group compared to survival group; thus, low FFMI emerged as a risk factor for mortality associated with COPD. Given that FFMI serves as an indicator of muscle mass and nutritional status, it follows that COPD patients exhibiting muscle atrophy and inadequate nutritional status face an elevated risk of death.[44,45] Patients with low FFMI often experience a decline in quality of life,[39] reduced exercise capacity, impaired lung function, performance deterioration of respiratory muscle, and exacerbated dyspnea,[46] all contributing to heightened mortality risks. While nutritional status correlates with poor prognosis such as AE and mortality in COPD patients,[47] early identification of nutritional deficits and implementation of individualized interventions remain challenging. Moreover, although FFMI independently predicts adverse outcomes in adjusted models, residual confounding cannot be excluded, necessitating randomized trials that directly manipulate FFMI to establish causality. Meanwhile, there is a lack of sufficient research evidence to elucidate the relationship between nutritional status, inflammatory response, and immune function in patients with COPD.

In this study, we acknowledge several limitations. (1) Due to the small number of studies involving FFMI and COPD, the results of subgroup analyses need to be validated by more high-quality prospective studies in the future. And future meta-analyses with ≥10 studies should test covariates (age, FEV_1%, smoking dose) via meta-regression to quantify heterogeneity sources. (2) Limited by study design, future studies may consider pooled analyses to clarify the association between inflammatory status, mobility, quality of life, and nutritional status in patients with COPD. (3) Our pooled study was unable to determine the diagnostic value and cut-off value of FFMI across different stages of COPD and associated poor prognosis. (4) Two included studies were of medium quality, which may introduce the risk of bias into our results; nevertheless, further sensitivity analysis, Egger's test and funnel plot of trim-and-fill method showed that our findings were stable and reliable. (5) While Egger's test, funnel plots, and the trim-and-fill method were employed to assess publication bias, we acknowledge that these approaches may have reduced sensitivity in meta-analyses with a limited number of studies. However, the stability of our findings was corroborated by Egger's test and symmetrical funnel plots.

Conclusion

Low FFMI serves as a significant indicator of disease status and poor prognosis in patients with COPD. These findings underscore the importance of routine FFMI assessment in clinical settings and highlight the need for longitudinal

controlled trial studies to explore whether nutritional or muscle-preserving interventions can improve outcomes in this population.

Data Sharing Statement

The original data presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Consent to Publication

Authors are all agreed to publication.

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Author contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest in this work.

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