Respirology

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Official Journal of the Asian Pacific Society of Respirology
Respirology
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EDITORIAL

Assessment of the Risk of Severe COPD Exacerbations: Balancing Between Fat and Muscle

Felipe V. C. Machado[1,2] | Kenneth Verboven[1,2] | Frits M. E. Franssen[3,4,5]

[1]REVAL-Rehabilitation Research Centre, Hasselt University, Diepenbeek, Belgium | [2]BIOMED-Biomedical Research Institute, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium | [3]Department of Research and Development, Ciro, Horn, the Netherlands | [4]NUTRIM School of Nutrition and Translational Research in Metabolism, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, the Netherlands | [5]Department of Respiratory Medicine, Maastricht University Medical Centre (MUMC+), Maastricht, the Netherlands

Correspondence: Felipe V. C. Machado (felipe.machado@uhasselt.be)

Received: 31 January 2025 | **Accepted:** 9 February 2025

Funding: The authors received no specific funding for this work.

Keywords: body composition assessment | COPD exacerbations | fat distribution | sarcopenic obesity

In all stages of the disease, individuals with chronic obstructive pulmonary disease (COPD) are at risk of exacerbations—acute respiratory events characterised by a worsening of respiratory symptoms [1]. These exacerbations can be triggered by various factors, including bacterial or viral respiratory infections, environmental pollutants, or unidentified causes, frequently associated with heightened local and systemic inflammation [1]. Exacerbations significantly impact patients' health status and prognosis, necessitate specific preventive and therapeutic measures, often result in hospitalisations, and represent the largest share of the overall COPD burden on healthcare systems [1]. Numerous efforts have been made to develop risk scores for predicting COPD exacerbations, utilising routinely available predictors such as age, smoking status, lung function, body mass index (BMI) and medication use [2]. While BMI is often included in these models, there is growing evidence that it should be replaced with measures of body composition to better capture their independent contributions to the incidence of exacerbation in patients with COPD.

Previous studies demonstrated associations between BMI and measures of body composition, such as fat-free mass index (FFMI), and exacerbations in patients with COPD [3–5]. For instance, a recently proposed subgroup—the multi-organ loss of tissue COPD phenotype—is characterised by more severe emphysema, greater airflow limitation, lower BMI and FFMI. This phenotype has also been linked to increased exacerbation risk [4]. Conversely, whether obesity reduces or increases the risk of exacerbations remains debated [5], possibly because most studies fail to include direct measures of body fat quantity and distribution.

In a recent publication in Respirology, Yuanyuan et al. employed logistic regression analysis to assess the risk of severe COPD exacerbations in 631 patients, evaluating the impact of increases in various body composition variables assessed by bioelectrical impedance analysis and anthropometry [6]. After a median follow-up of 62 months, 186 patients (29.5%) experienced a severe COPD exacerbation within 1 year, and 304 patients (48.2%) had severe exacerbations within 5 years. The authors presented hierarchical models adjusted for several potential confounders. In these models, BMI and variables representing isolated measures of fat, such as visceral fat area, waist circumference or muscle mass alone, showed less robust associations with exacerbation risk. In contrast, a combined variable incorporating markers of fat and muscle mass (i.e., the visceral fat-to-muscle mass ratio) demonstrated stronger associations with exacerbation incidence across all models.

While this study provides valuable insights into the role of body composition in COPD exacerbation risk, the use of bioelectrical impedance analysis (BIA) to assess regional body composition is a limitation. This method can be subject to inaccuracies due to assumptions about body shape and variability in the equations used to estimate muscle mass [7, 8]. Furthermore, some BIA-derived variables lack reference values that adequately account

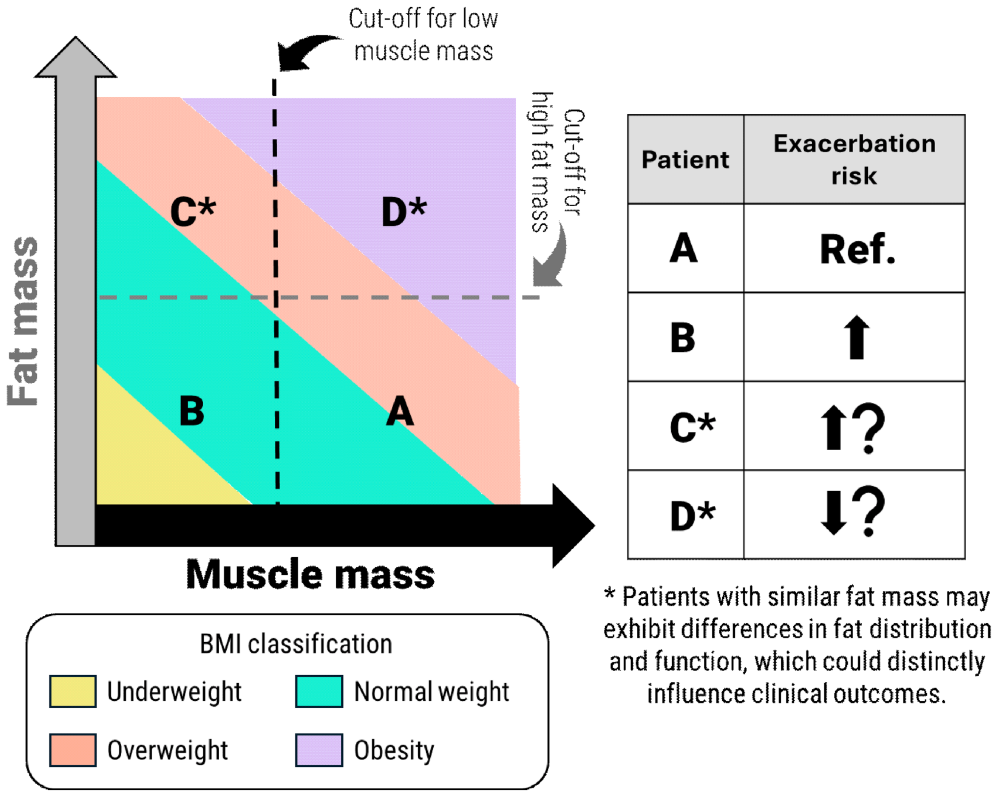

FIGURE 1 | Theoretical framework illustrating the potential impact of body composition on COPD exacerbation risk.

for sex and age differences, and there is currently a lack of validation studies in COPD populations. Additionally, although the follow-up duration of 1 and 5 years is appropriate, it is noteworthy that the observed incidence of severe exacerbations appears higher than expected, especially considering the relatively preserved lung function in this cohort (predominantly mild-to-moderate airflow obstruction) that was not selected based on exacerbation history. The authors conducted a sensitivity analysis to exclude patients with concurrent pneumonia and acknowledged that some exacerbations might have been misdiagnosed, potentially attributed to comorbid conditions such as heart failure. Additionally, a limitation of the study is the absence of data on mild and moderate exacerbations and the lack of adjustment for COPD medications. Consequently, further studies are required to better understand the impact of fat and muscle mass imbalances on COPD exacerbation risk.

A key takeaway from this study is the importance of assessing body composition holistically, considering both fat and muscle mass, regardless of whether accessible or advanced methods are used. Multiple studies highlight the value of screening for sarcopenic obesity and assessing relative adequate muscle. These studies suggest that defining abnormally low muscle mass requires accounting for factors such as adiposity level and/or total body weight [7, 8]. Furthermore, in patients with COPD, the impact of low FFMI on clinical outcomes may vary depending on BMI. This has been demonstrated in relation to exercise capacity, quality of life and systemic inflammation [9], although its role in COPD exacerbations remains unclear. Additionally, higher fat mass may be less clinically significant depending on its distribution and the absence of objective clinical signs of organ dysfunction or impairments in daily activity performance [10].

To illustrate the potential relationship between body composition and COPD exacerbation risk, we propose a theoretical framework in Figure 1, integrating current knowledge with new insights from Yuanyuan et al. [6]. This scheme categorises patients into four quadrants based on body composition. In this model, individuals with normal body composition (A) serve as the reference group, with exacerbation incidence influenced by other predictors of COPD exacerbations. We recognise that this quadrant-based framework requires validation. However, existing evidence suggests that patients with low BMI and/or low muscle mass (B) are at an increased risk of exacerbation. Conversely, we raise the question of whether individuals with high fat mass, with (C) or without (D) concurrent muscle loss, exhibit distinct exacerbation risks. Given that many studies rely on BMI as a primary metric, our framework highlights its potential confounding effect—patients classified within the same BMI category may, in fact, belong to different quadrants, with potentially different exacerbation risks. Additionally, beyond the absolute amount of fat mass, its distribution may also play a critical role in exacerbation risk and should be considered in future studies.

Conflicts of Interest

F.V.C.M. and K.V. declare no conflicts of interest. F.M.E.F. has received consulting fees from Sanofi and MSD in the past 36 months. Additionally, F.M.E.F. has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from AstraZeneca, Chiesi, GSK, Sanofi and Pfizer. F.M.E.F. has also received support for attending meetings and/or travel from AstraZeneca. However, none of these relationships present a conflicts of interest concerning this manuscript. F.M.E.F. 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.

Linked Content

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