Review Article

Quantitative CT evaluation of extrapulmonary lesions in chronic obstructive pulmonary disease: a narrative review

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Background and Objective: Chronic obstructive pulmonary disease (COPD) is a significant global health challenge characterized by persistent respiratory symptoms and airflow limitation. Recent advancements in computed tomography (CT) have enhanced our understanding of COPD, particularly in diagnosing extrapulmonary comorbidities. This review aims to summarize the current findings on extrapulmonary manifestations in COPD patients and the role of quantitative computed tomography (QCT) in evaluating these comorbidities.

Methods: A comprehensive literature search was conducted using PubMed and Web of Science databases, covering studies from January 1999 to May 2024. Keywords included "COPD", "chronic obstructive pulmonary disease", "muscle", "adipose tissue", "coronary artery calcification", "bone density", "extrapulmonary manifestations", and "Quantitative Computed Tomography". Inclusion criteria focused on studies involving COPD patients using QCT to identify extrapulmonary manifestations, published in peer-reviewed journals and available in English.

Key Content and Findings: The review highlights significant findings, such as the reduction in muscle mass and bone density and the increase in coronary artery calcification (CAC) in COPD patients, all closely associated with disease severity and prognosis. Key metrics evaluated include mid-thigh muscle cross-sectional area, pectoralis muscle area, erector spinae muscles, and bone density. Advanced CT analysis techniques, including artificial intelligence (AI) and machine learning, are emphasized as crucial for improving assessment accuracy and efficiency. Subcutaneous fat reduction and CAC are identified as critical indicators of mortality and disease progression.

Conclusions: Quantitative CT evaluation is vital for understanding and managing extrapulmonary lesions in COPD. Future research should focus on establishing suitable measurement tools and methods and defining critical thresholds for treatment efficacy. The integration of advanced CT techniques and interdisciplinary approaches is essential for enhancing diagnostic accuracy and developing personalized treatment strategies for COPD patients.

Keywords: Chronic obstructive pulmonary disease (COPD); lung imaging; computed tomography (CT)

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Introduction

Chronic obstructive pulmonary disease (COPD) is a complex and heterogeneous disease (1). Currently, the World Health Organization considers COPD as the third leading cause of death globally (2), predicting that over 2.9 million people die annually due to COPD and its complications (3). Characterized by limited airflow, COPD poses a significant challenge to global public health (4).

In recent years, advancements in medical imaging technology, particularly in the application of computed tomography (CT), have significantly enhanced the research and understanding of COPD (5). COPD often coexists with other diseases, some of which can influence the progression of COPD (1). CT not only provided detailed views of lung structures but also revealed extrapulmonary changes related to COPD, such as alterations in muscle tissue, fat distribution, bone density, and coronary artery changes, indicating the effects of extrapulmonary manifestations. These extrapulmonary presentations were crucial for understanding the comprehensive impact of COPD, improving patient management strategies, and optimizing treatment plans. A comprehensive literature review spanning the past 25 years was conducted using the PubMed and Web of Science databases. Following an extensive analysis and critical discussion of the retrieved studies, this review was subsequently completed.

In the field of COPD research, the diagnosis and exploration of extrapulmonary comorbidities not only focused on revealing the various disease characteristics and pathophysiological changes accompanying different individuals but also strived to correlate these characteristics with clinically significant outcomes. These include key indicators such as acute exacerbation of COPD, the ongoing deterioration of the disease, and mortality risk. Therefore, a significant number of articles in this field use prospective design methodologies to rigorously verify and quantify the analysis of every possible extrapulmonary manifestation and its relationship with COPD prognosis, aiming to provide more precise and comprehensive patient disease management strategies.

However, comprehensive analyses of extrapulmonary comorbidities of COPD using CT were relatively scarce in the literature. It was noted that most extrapulmonary manifestations shared common characteristics of chronic systemic inflammation, which all increase the incidence of COPD (6).

According to the content released by Global Initiative for Chronic Obstructive Lung Disease (GOLD)2024, CT can provide extensive information on extrapulmonary manifestations, including muscle mass, bone density, fat area, and coronary calcification (*Table 1*). We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1074/rc).

Methods

A comprehensive literature search was conducted to identify studies on extrapulmonary manifestations of COPD as observed through quantitative computed tomography (QCT). Utilizing PubMed and Web of Science databases, the search encompassed publications from January 1999 to May 2024. Keywords such as "COPD", "chronic obstructive pulmonary disease", "muscle", "adipose tissue", "coronary artery calcification", "bone density", "extrapulmonary manifestations", and "Quantitative Computed Tomography" were employed. Inclusion criteria focused on studies involving COPD patients, using QCT to identify extrapulmonary manifestations, published in peer-reviewed journals, and available in English (*Table 2*, Table S1).

Literature search and screening results

Using databases such as PubMed and Web of Science, a total of 221 articles were initially identified for further screening. Among these, 81 duplicate studies were excluded. Each article was evaluated based on its title and abstract, leading to the exclusion of studies with inconsistent populations and case reports. Ultimately, 41 studies pertinent to the research topic were identified (Figure S1).

CT measurement of muscle mass

The term "muscle mass" referred to a concept rather than a specific muscle. The relevance of muscle to COPD can be traced back to the correlation between the cross-sectional area of leg muscles and the survival rate of COPD patients. It was believed that the cross-sectional area of leg muscles has a closer relationship with patient survival compared to body weight (9). The pectoralis muscle, often studied, was measured by CT in terms of its cross-sectional area, which was thought to predict disease progression (10-14) and was related to systemic inflammation (*Figure 1*) (15). Some researchers have measured the erector spinae muscles (7,12,16) and the bilateral psoas muscles (8), all of which

Table 1 Summary of the application of quantitative indicators for extrapulmonary complications based on computer tomography in research

Quantitative metric	Definition	Comments
Midthigh muscle cross-sectional area	Obtained from CT scans of the thigh between the pubic symphysis and the femoral condyle	Related to predicting mortality
Pectoralis muscle area	Area of the pectoral muscle measured in the first axial image immediately above the aortic arch	Positively correlated with lung function; predicts disease progression
Erector spinae muscles	Measurement of the muscle area of erector spinae at the level of the 12th thoracic vertebra	Related to predicting mortality (7)
Paoas muscles	Measured area of the left and right psoas muscles at the level of the third lumbar vertebra	Related to predicting mortality (8)
Bone density (use mineral reference phantom)	Measured bone mineral density of three consecutive thoracic vertebrae from a section containing the caudal side of the left coronary artery	Low bone density was associated with fracture risk and mortality
Bone density (no mineral reference phantom)	Average bone attenuation of thoracic vertebrae T4, T7, and T10 measured in HU	Low bone density was associated with fracture risk and mortality; negative correlation with the degree of emphysema
Adipose tissue	Defined by measuring the area between the pectoralis major muscle and skin surface, identifying subcutaneous fat	Decrease in subcutaneous fat was related to increased mortality, while intramuscular fat has the opposite effect

CT, computed tomography; HU, Hounsfield unit.

Table 2 The search strategy summary

Items	Specification
Date of search	June 10, 2024
Databases and other sources searched	PubMed and Web of Science databases
Search terms used	COPD-related terms: "COPD" (MeSH), "chronic obstructive pulmonary disease" (free text)
	Extrapulmonary Manifestations Terms: "muscle" (MeSH), "muscle" (free text), "adipose tissue" (MeSH), "adipose tissue" (free text), "coronary artery calcification" (MeSH), "coronary artery calcification" (free text), "bone density" (MeSH), "bone density" (free text), "extrapulmonary manifestations" (free text)
	CT-related terms: "Quantitative Computed Tomography" (MeSH), "Computed Tomography" (free text), "CT" (free text)
Timeframe	January 1, 1999 to May 31, 2024
Inclusion and exclusion criteria	Inclusion criteria: research involving patients with chronic obstructive pulmonary disease; using nuclear medicine related equipment (such as X-rays, CT) to identify extrapulmonary manifestations; published in peer-reviewed journals; there was an English version available
	Exclusion criteria: the study does not focus on the extrapulmonary manifestations of chronic obstructive pulmonary disease; research does not use nuclear medicine related equipment (such as X-rays, CT) as diagnostic tools; review articles, case reports, conference abstracts, or editorials; there was no English version available for the research
Selection process	The selection process was independently conducted by two respiratory doctors, C.M. and F.W. Any differences were resolved through discussion or negotiation with a third, more experienced respiratory specialist, R.C., to reach a consensus

COPD, chronic obstructive pulmonary disease; CT, computed tomography; MeSH, medical subject headings.

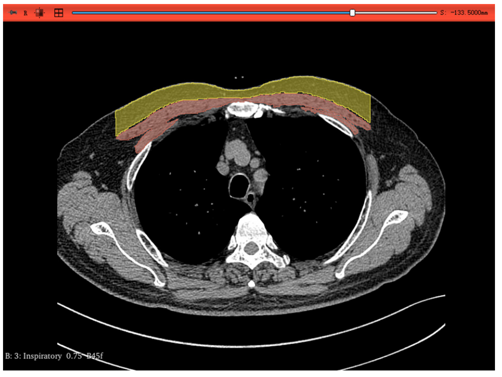

Figure 1 Body composition phenotypes. Manual segmentation of pectoralis muscles (red) and subcutaneous adipose tissue (yellow) at the level of the aortic arch.

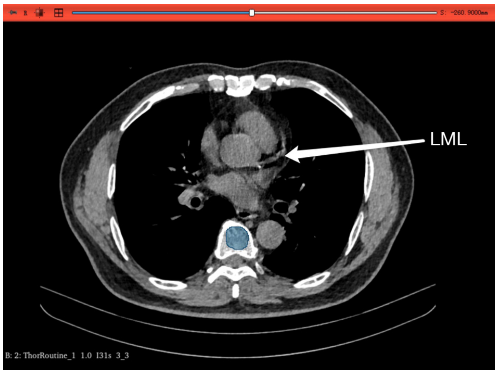

Figure 2 Bone mineral density measurement on thoracic quantitative CT images. The blue area in the image represents the measurement values marked on the axial section. CT, computed tomography; LML, left main coronary artery level.

were associated with the mortality rate of COPD patients. Compared to the cross-sectional area of the pectoralis muscles, the erector spinae muscles were believed to have a more significant relationship with the mortality rate in COPD patients (12).

Interestingly, pectoral muscle area (PMA), as a non-respiratory muscle, participated in assisting respiration and was considered related to lung function (11,12,14,17). This may be due to a decline in lung function in COPD patients, leading to increased muscle catabolism, muscle atrophy, and overall fatigue (17), although a study does not associate lung function decline with COPD (18). This could be due to differences in inclusion criteria, with some teams mostly including patients in the early to middle stages of COPD, where muscle loss was less (17); or due to variations in patient positioning, affecting the results of the analysis; additionally, different CT measurement locations can also lead to varying results. With age, muscle area and density decrease, which also impacts our measurements, and this decline was faster in COPD patients (19). Excessive chemotaxis of neutrophils and heightened extracellular protease activity may reflect the significant effects of lung inflammation on systemic circulation, skeletal muscle, and bone marrow, potentially leading to the induction or exacerbation of comorbidities such as sarcopenia associated with COPD (20).

CT measurement of bone density

At the initial stage of using CT to assess bone mineral density (BMD), people will use a mineral reference (bone) phantom to scan CT with patients to ensure that the measured Hounsfield unit (HU) value can be converted into reference values such as BMD (21-23). However, more and more studies have shown that HU value was closely related to BMD, and BMD can be determined only by HU value (24,25). Some studies may choose the left main coronary artery level (LML) as the entry point to measure the HU value of the region of interest (21,22,25,26) (*Figure 2*), while others may choose to measure the HU value of the region of interest of thoracic (T) 4, T7, T10, and first lumbar vertebra (24,27,28). Both of these measurement methods were widely accepted.

In the 1970s, the Hounsfield-developed clinical CT provided precise information on tissue density from X-ray attenuation, making it akin to a scanner. Nowadays, most studies measuring bone density using CT utilize bone attenuation values, which, in comparison to dual-energy X-ray absorptiometry (DXA), made CT more practical (29), and even better at identifying low bone density than DXA (30). Bone density was considered closely related to low bone density and fracture risk in most studies (10,23), and low bone density was associated with mortality (25,31). Interestingly, a study has found no relationship between bone density and all-cause mortality (24). The conclusions of these studies may vary due to differences in sample characteristics and size, with patient groups differing in age, sex, disease severity, and other health conditions.

COPD patients generally experienced significant oxidative stress, with excessive free radical production and accumulated cellular damage, not only harming lung tissue but also potentially disrupting the balance of bone cells, leading to a decline in bone density (32). In an earlier study using CT to measure bone density, it was believed that bone density had a negative correlation with emphysema indicators (28). In 2012, the team discovered that subjects with a history of acute exacerbations exhibited a greater decline in thoracic vertebral BMD compared to those without such a history (33). Additionally, Graumam found a correlation between bone density and a decline in forced expiratory volume in 1 second (FEV1) (34). However, Kenichi Goto's 2018 publication argued that bone density was not related to FEV1 (35), possibly due to differences in testing methods: Graumam used DXA technology to measure lumbar spine, femoral neck, and total femur density (34), while Goto used CT to measure the attenuation value of all thoracic vertebrae (35).

Their inclusion criteria and statistical methods also differed, leading to different measurement results. Overall, CT's application in assessing bone density in COPD patients has shown unique advantages. It not only reflects pathological changes in the skeletal system of COPD patients but also aids in predicting the prognosis and risk of complications. Although in some cases, the method of assessing bone density with thoracic vertebral CT remains limited in its accuracy and inability to cover all osteoporosis-related factors comprehensively, its convenience in clinical practice and the potential for concurrent assessment with lung disease make it a promising evaluation tool.

Measurement of adipose tissue

In some studies, the measurement of fat was conducted simultaneously with the measurement of the pectoral muscles, as the chosen cross-sections were the same, most commonly at the level of the sternal notch, which was easily accessible (*Figure 1*) (15,36). A reduction in subcutaneous fat has been associated with an increased mortality rate, whereas the role of intermuscular fat appears to be the opposite (37). In fat-related research, gender factors were considered, revealing a significant association between the area of subcutaneous fat and the concentration of C-reactive protein and fibrinogen in the blood ($r=0.51$) (15). This could be due to the dysfunction of adipose tissue, such as a state of chronic low-grade inflammation, which might affect the immune response in the lungs and promote airway hyperreactivity (38).

Measurement of coronary artery calcification (CAC)

Cardiovascular diseases accounted for the majority of deaths in mild to moderate COPD, with most patients being asymptomatic (39). Long-standing hypoxemia and limited respiratory function in COPD patients further increase the risk of cardiovascular disease (40). In the intrinsic connection between COPD and coronary artery disease (CAD), both shared several pathophysiological mechanisms, such as endothelial dysfunction and increased arterial stiffness (6). Over-inflation of the lungs, leading to decreased efficiency of the respiratory muscles and respiratory distress, together with systemic inflammation and oxidative stress, promotes the development and progression of arteriosclerosis (41). Moreover, the acute exacerbation of COPD was related to the increase of cardiovascular disease (42).

A study indicated that CT imaging of CAC provided a more effective risk assessment than scoring systems used in the general population (43). Williams found that the coronary artery calcification score (CACS) was not related to emphysema and lung function, but an increase in CACS was associated with an increased mortality rate in COPD patients (44). In the article published in 2011, it was mentioned that electrocardiogram (ECG)-gated and non-gated CT were almost equally accurate in measuring thoracic aortic calcification (45). Research teams, through baseline CT scans, assessed Agatston and Weston scores, finding an inverse relationship between FEV1 and Agatston score for coronary calcification, with visual scoring of CAC related to airflow obstruction and cardiovascular events. The team also believed that visual scoring was more applicable in clinical practice (39).

However, coronary angiography remains the gold standard for the assessment of CAD. But CT examination plays a significant role in early screening and risk prediction of coronary arteriosclerosis in patients, and can reduce the cost of examination.

Future research directions

CT was becoming increasingly important in the diagnosis and treatment of COPD, particularly regarding its

Table 3 Summary of sample size and results of typical article research design

Study focus	Study design	Sample sizes	Key findings related to COPD
Cross-sectional area of leg muscles (9)	Prospective cohort	142 COPD patients	Significant predictor of mortality rate
Pectoralis muscle	Prospective cohort (14)	1,352 subjects	Positive correlation with lung function
	Cross-sectional observational study (10)	Two queues totaling 1,309 subjects	Significant correlation with lung function, dyspnea, and 6-minute walking distance
Spinae muscles (49)	Prospective cohort	150 subjects	Significantly correlated with previously reported prognostic factors
Psoas muscles (8)	Prospective cohort	220 COPD patients	Variables independently correlated with all-cause mortality rate
T4, T7, T10, and L1 bone density (28)	Cross-sectional observational study	65 male COPD patients	Correlated with the extent of pulmonary emphysema significantly
Bone density at the left main coronary artery (25)	Prospective cohort	322 subjects	Significant correlation between patient mortality and disease severity
Adipose tissue (37)	Prospective cohort	2,994 subjects	Negative correlation with mortality rate
Coronary artery calcification (44)	Prospective cohort	942 subjects	Associated with increased dyspnoea, reduced exercise capacity and increased mortality

COPD, chronic obstructive pulmonary disease.

extrapulmonary manifestations (46). Recent advancements have highlighted CT's role in assessing disease progression and treatment response (47). While routine clinical examinations may overlook extrapulmonary signs, CT images provide crucial insights, especially in predicting patient mortality and detecting latent issues early (48) (*Table 3*).

However, there were significant challenges in current practices, including the variability in interpreting CT findings and the potential for missed diagnoses of extrapulmonary complications (49). These limitations underscore the need for improved diagnostic tools.

In this context, the integration of artificial intelligence (AI) techniques presents a promising solution. AI can enhance the analysis of CT images, improving the accuracy of extrapulmonary manifestation detection and enabling better risk stratification for patients (48). By automating and standardizing image analysis, AI can help overcome the subjective nature of traditional assessments.

Currently, a significant breakthrough was reported in a 2023 academic paper by the research team led by Professor Daniel Genkin, who developed an innovative process for the fully automatic extraction of PMA from chest CT scans (50). This advanced automated processing pipeline successfully achieves precise identification of CT slices at the level of the aortic arch and nearly perfectly simulates the manual segmentation technique of the pectoralis major muscle, with results nearly indistinguishable from manual operations. This key technological breakthrough significantly advances the automation process of muscle quantification, making it more convenient to assess muscle mass in the future.

The future research trend and technological development in this field were characterized by multi-dimensionality, precision, and intelligence. Scientists were dedicated to developing and perfecting advanced CT analysis methods aimed at providing one-stop solutions for simultaneous assessments of multiple systems such as pulmonary, cardiovascular, skeletal, and muscular. Systemic indicators like CAC, thoracic aorta calcification (51,52), bone density, and muscle mass were expected to be more comprehensively analyzed in a single CT scan, deeply revealing the overall health status of COPD patients.

The development of intelligent automation technology has become a key driving force in this area, especially through the creation of fully automated or semi-automated analysis platforms integrating AI and machine learning algorithms (53). Such platforms can accurately extract and quantify various extrapulmonary disease indicators from chest CT images, such as pectoralis major area, subcutaneous fat, visceral fat, and bone density, thereby significantly reducing human error and enhancing diagnostic accuracy and efficiency.

Interdisciplinary research was deepening, exploring the intrinsic connections between COPD and other chronic diseases such as cardiovascular disease, osteoporosis, and muscle atrophy, and using CT imaging to find new early warning biomarkers and prognostic indicators to provide a scientific basis for developing personalized treatment strategies (54).

Moreover, by delving deeper into CT data, researchers will further reveal the close relationship between extrapulmonary manifestations and the prognosis of COPD patients, including core elements such as survival rate, incidence rate, and quality of life. Based on this, treatment plans and prevention strategies can be optimized, pushing disease management towards greater precision.

Based on the systemic disease information obtained from CT assessments, researchers can finely stratify risks for COPD patients, designing targeted individualized treatment plans for different types of patients (55). For example, specific interventions can be implemented for COPD patients with concurrent osteoporosis, and appropriate nutritional supplements and exercise therapies can be recommended for patients with decreased muscle mass.

Technological advancements will also promote the development of real-time monitoring and long-term tracking techniques, using advanced dynamic CT imaging technology and rigorous follow-up protocols to continuously and real-time monitor changes in the body composition of COPD patients, enabling timely adjustment of treatment plans and preventing complications.

To address the challenges in assessing extrapulmonary manifestations in COPD, it was essential to establish a standardized framework for CT analysis. Currently, inconsistencies in methodologies can lead to variability in results, undermining the reliability and comparability of findings across studies. Thus, standardization and normalization of CT analysis processes were critical. By implementing unified standards and guidelines, we can enhance the consistency of CT assessments globally, making them widely recognized and adopted.

Furthermore, another significant issue was the lack of standardization for normal and reference values related to muscle assessments in CT. This gap highlights the necessity for a comprehensive review that explores reference values and their implications in clinical practice. Addressing these standardization issues not only clarifies existing problems but also paves the way for more accurate and universally applicable assessments in COPD research.

Conclusions

In summary, CT was becoming increasingly important in the diagnosis and treatment of COPD, and its importance in extrapulmonary manifestations was equally significant. In recent years, CT has been widely used to assess the progression of COPD and its response to treatment. Through this comprehensive analysis, we recognize that even though extrapulmonary signs in COPD patients may not be easily detected in routine clinical examinations, they were clearly visible in CT images, especially in predicting patient mortality risk and early detection of latent issues. Further exploration and analysis of extrapulmonary manifestations, based on a detailed assessment of pulmonary changes, will aid in devising more accurate and effective treatment plans for patients. Given the importance of CT in diagnosing extrapulmonary manifestations of COPD, more scientific research is urgently needed to determine the most suitable measurement tools and methods and define critical thresholds that reflect treatment efficacy.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1074/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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