Diffusing Capacity of the Lung for Carbon Monoxide in Chronic Obstructive Pulmonary Disease: Clinical Application and Research Progress (Postprint)

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Abstract

Pulmonary function testing, as the "gold standard"for grading and therapeutic efficacy evaluation in chronic obstructive pulmonary disease (COPD), constitutes a core modality for COPD diagnosis and management. While lung ventilation function indicators can effectively reflect the degree of airway obstruction, they are limited in their ability to early identify pulmonary parenchymal injury and microvascular pathology. In contrast, diffusing capacity of the lung for carbon monoxide (DLCO) represents a crucial parameter for assessing pulmonary gas exchange function, which demonstrates rapid responsiveness during the early stages of COPD and provides important clues for early disease recognition. This article systematically examines the utility of DLCO in COPD patients across early disease identification, disease severity stratification, acute exacerbation risk, and long-term prognosis, summarizing the distinctive value of DLCO in COPD and its comorbidities. The present study indicates that in clinical practice, DLCO may serve as an alternative indicator for disease assessment or prognostication in patients unable to complete lung ventilation function testing due to factors such as poor pulmonary function and advanced age. For COPD patients with comorbid pulmonary hypertension, heart failure, and lung cancer, DLCO can effectively identify comorbidity severity or facilitate prognostic determination. This article provides a reference for DLCO research in COPD patients with comorbidities.

Full Text

Clinical Application and Research Progress of Diffusing Capacity of the Lung for Carbon Monoxide in Chronic Obstructive Pulmonary Disease

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Abstract

Pulmonary function testing, regarded as the "gold standard" for the classification and evaluation of therapeutic efficacy in chronic obstructive pulmonary disease (COPD), is a core method for its diagnosis and management. Among these tests, pulmonary ventilation parameters can effectively reflect the degree of airway obstruction; however, they are limited in detecting early lung parenchymal damage and microvascular lesions. In contrast, the diffusing capacity of the lung for carbon monoxide (DLCO) is an important indicator of pulmonary gas exchange function, which responds sensitively in the early stages of COPD and provides valuable clues for early disease detection. This article systematically discusses the role of DLCO in the early identification of COPD, assessment of disease severity, risk of acute exacerbations, and long-term prognosis, and summarizes its unique clinical value in COPD and related comorbidities. DLCO may serve as an alternative indicator for disease evaluation or prognostic assessment in patients with poor lung function or advanced age who are unable to complete pulmonary ventilation testing. Furthermore, in patients with COPD complicated by pulmonary hypertension, heart failure, or lung cancer, DLCO can effectively reflect the severity of comorbidities and assist in prognostic evaluation. This review provides a useful reference for future studies on DLCO in patients with COPD and its comorbid conditions.

Keywords: Chronic obstructive pulmonary disease; Diffusion capacity of lung for carbon monoxide; Review

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Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic airway disease characterized by persistent airflow limitation and respiratory symptoms [1], with high prevalence, mortality, and economic burden. Early prevention, diagnosis, and standardized treatment play an irreplaceable role in COPD control [2]. According to WHO statistics [3], COPD affects over 380 million people globally, including nearly 100 million patients in China. In 2021 alone [4], there were approximately 16.9 million new COPD cases worldwide, with 3.7 million deaths. Epidemiological studies predict that from 2020 to 2050, COPD will cause global economic losses of up to $4.326 trillion, with China and the United States bearing the primary burden [5].

Pulmonary function testing is the gold standard for COPD diagnosis [6], primarily including lung volume parameters, ventilation function parameters, and lung diffusion capacity parameters. In early COPD stages [7], forced expiratory volume in 1 second (FEV1) is not sensitive to airway obstruction, and using the FEV1/FVC ratio often leads to overdiagnosis in elderly populations [8] and missed diagnosis in younger patients. Lung diffusion capacity is an important parameter reflecting pulmonary gas exchange capability. As a core indicator, the diffusing capacity of the lung for carbon monoxide (DLCO) measures the rate of carbon monoxide transfer from alveoli to capillaries [1] and offers unique advantages in early disease identification, symptom assessment, exercise tolerance evaluation, and prognosis determination. Research has found that when pulmonary ventilation function is normal, decreased diffusion function increases COPD susceptibility and accelerates lung function deterioration [9-10], suggesting that diffusion parameters have important value in early disease identification. The latest Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2025 [1] also recommends DLCO measurement for patients with clinical symptoms inconsistent with the degree of airflow obstruction to further assess disease status and risk. This study aims to systematically explore the clinical application status of DLCO in COPD and analyze its evaluation value across different disease stages and comorbidity states.

Literature search strategy: English databases (PubMed, Web of Science, Embase) were searched using keywords "Respiratory Function Tests, Lung Function, DLCO, Chronic Obstructive Pulmonary Diseases, COPD" ; Chinese databases (CNKI, Wanfang, VIP, SinoMed) were searched using keywords "慢性阻塞性肺疾病, COPD, 一氧化碳弥散量, DLCO". The search period was from database inception to July 11, 2025. Inclusion criteria: literature reporting DLCO in pa-

tients meeting COPD diagnostic standards. Exclusion criteria: studies with insufficient data, duplicate publications, unavailable full text, or poor quality.

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1. Definition and Measurement Methods of DLCO

DLCO is a core indicator for assessing alveolar-capillary membrane gas exchange capacity, primarily measured through single-breath carbon monoxide diffusion testing and rebreathing methods. DLCO results are influenced by multiple physiological and pathological factors, including age [11], height [12], body weight [13], gender, race [14], body position [15], hemoglobin concentration [16], and cardiac function status [11]. In recent years, with advances in pulmonary function assessment technology, DLCO has gradually become an important clinical tool for evaluating lung function due to its simplicity, sensitivity, and high repeatability [17].

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2. Application of DLCO in COPD

2.1 Early Identification of COPD DLCO is a key indicator for evaluating pulmonary diffusion function in COPD patients, quantifying the reduction in diffusion area and pulmonary blood flow disturbances caused by emphysema. In pre-COPD or preserved ratio impaired spirometry (PRISm) populations, DLCO also demonstrates potential identification value, and research shows that early intervention in COPD may halt or reverse disease progression [18].

In smokers without airflow limitation, decreased DLCO is associated with higher COPD prevalence, reduced exercise capacity, and pulmonary artery dilation [19], suggesting that DLCO may serve as a surrogate marker for smoking-induced early vascular lung injury with potential value in identifying pre-COPD. COSÍO et al. [20] identified emphysema, bronchial wall thickening, and DLCO decline as markers of pre-COPD, finding that 22.3% of the general population met these criteria. DLCO decline is also an important marker for PRISm progression to COPD [18]. OGATA et al. [21] noted that approximately half of PRISm patients have decreased DLCO, with more severe impairment than in mild-to-moderate COPD, and DLCO levels show a linear relationship with mortality risk, suggesting that DLCO assessment should be incorporated into PRISm prognosis evaluation. However, some studies have found that DLCO impairment is not significantly associated with annual decline rates of FEV1, forced vital capacity (FVC), or FEV1/FVC, and its sensitivity for COPD incidence in patients with normal spirometry is low, making it an ineffective discriminatory indicator [22]. In summary, while DLCO has certain specificity, it has limitations as a single screening indicator and requires combined assessment with pulmonary function, imaging, and clinical manifestations to evaluate its application value in early COPD identification.

2.2 Assessment of Disease Severity In COPD, emphysema is the main cause of DLCO impairment [23-24], and its severity closely correlates with the degree of DLCO reduction. Emphysema-induced lung parenchymal destruction and loss of pulmonary capillary beds [25] explain the association between DLCO and symptom severity in COPD patients.

In mild COPD stages [26], airway obstruction may not be apparent, but pulmonary microvascular lesions emerge early, causing reduced or dysfunctional pulmonary vascular beds, leading to decreased diffusion capacity, manifesting as exertional hypoxia, dyspnea, and reduced exercise tolerance. In mild COPD patients with DLCO below 60% predicted [27], malnutrition, lung hyperinflation, and decreased exercise capacity are common. Additionally, research indicates that mild COPD patients experience significantly worsened dyspnea during exercise [28], suggesting DLCO can serve as an indicator for assessing disease severity in mild COPD.

As COPD progresses to moderate-to-severe stages, DLCO effectively predicts exercise capacity [29] and, combined with inspiratory capacity (IC), can predict treatment response to inhaled corticosteroids/long-acting 2-agonists in moderate-to-severe COPD patients [30]. Numerous domestic and international studies demonstrate that DLCO is an important factor affecting exercise tolerance in COPD patients and can independently and accurately predict the risk of clinically important differences in 6-minute walk distance (6MWD) decline [31-34]. It should be noted that 6MWD is influenced by multiple parameters including DLCO, FEV1, and the inspiratory capacity to total lung capacity ratio (IC/TLC), with IC/TLC < 0.33 indicating significantly reduced exercise tolerance [35]. Meanwhile, DLCO decline is closely associated with respiratory symptoms in COPD patients [33,36-38], and low DLCO levels correlate significantly with symptom and quality-of-life scores, including the COPD Assessment Test (CAT), St. George' s Respiratory Questionnaire (SGRQ), and Short Form-36 Health Survey (SF-36), further supporting its comprehensive value in disease assessment.

Therefore, in mild COPD, despite minimal airway obstruction, DLCO decline can indicate pulmonary vascular abnormalities and reduced exercise capacity, providing early assessment significance. In moderate-to-severe COPD, DLCO not only independently predicts exercise capacity decline and quality-of-life deterioration but also, when combined with IC, evaluates response to inhalation therapy.

2.3 Prediction of Acute Exacerbation and Mortality Risk DLCO is an important indicator for evaluating lung function in COPD patients and is closely associated with acute exacerbations [23,36,39], hospitalization rates [40], and mortality [41]. BALASUBRAMANIAN et al. [36] demonstrated based on the COPDGene cohort that patients with normal FEV1 but reduced DLCO had worse symptoms, poorer exercise tolerance, and higher acute exacerbation risk, suggesting DLCO can compensate for FEV1 limitations in disease identification

and should be incorporated into multidimensional risk assessment systems. Simultaneous severe reduction of both FEV1 and DLCO indicates more complex and severe disease than reduction of either parameter alone.

BALASUBRAMANIAN et al. [42] found that in COPD patients with pulmonary hypertension, DLCO was an independent predictor of survival, while FEV1 showed no predictive value. Further research revealed that incorporating DLCO into the BODE index improved prediction accuracy. BALASUBRAMANIAN et al. [41] analyzed the COPDGene study and found that each 10% predicted decrease in DLCO increased mortality risk by 28%, with predictive accuracy comparable to the BODE index. DLCO strongly predicts all-cause mortality in COPD patients, independent of BODE index and CT-detected emphysema severity, further supporting its inclusion in COPD prognostic models.

Cohort studies show that a 7.5% decrease in carbon monoxide transfer coefficient (KCO) percentage predicted in COPD patients is significantly associated with mortality risk within 18-54 months, indicating the importance of DLCO and related parameters in disease progression and long-term survival prediction [44]. Additionally, research shows that approximately one-third of COPD patients have disproportionately greater DLCO decline relative to FEV1, often accompanied by decreased arterial oxygen partial pressure (PaO2) and arterial carbon dioxide partial pressure (PaCO2), which correlates with higher long-term mortality [45]. Some severe COPD patients [46] have normal daytime PaO2 but develop nocturnal hypoxemia, which can progress to daytime hypoxemia, suggesting DLCO decline is closely related to abnormal arterial blood gases across circadian rhythms, though its correlation with blood gas parameters during hypoxia is weak [47].

Therefore, in clinical practice, for patients unable to complete pulmonary ventilation tests to obtain FVC and FEV1 data due to poor lung function or advanced age, DLCO can be selected as an alternative indicator for disease evaluation or prognosis.

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3. Application of DLCO in COPD Comorbidities

As a core pulmonary function parameter, DLCO also plays a key role in common COPD comorbidities. Epidemiological studies show that the prevalence of pulmonary hypertension (PH) in COPD patients ranges from 5% to 53% [48], heart failure (HF) incidence reaches 42% [49-50], and emphysema detection rate in lung cancer patients can reach 45.3% [51]. These diseases all involve lung parenchymal destruction [52], ventilation/perfusion mismatch [53], pulmonary vascular remodeling, or pulmonary congestion [54] at the pathological level, directly or indirectly impairing gas exchange function and causing DLCO decline. Therefore, DLCO can not only identify the presence of these diseases but also serve as an indicator of disease severity, progression trends, and long-term prognosis.

In COPD patients with PH (COPD-PH), DLCO and its derived ratio indicators play multidimensional roles in screening, assessment, and prognosis evaluation. Studies show that in COPD-PH patients, FEV1/DLCO ratio negatively correlates with 6MWD, with each unit increase associated with approximately doubled risk of severe PH (pulmonary vascular resistance, PVR > 5 WU), indicating its predictive value for right ventricular pressure load and exercise limitation [55-56]. The FVC/DLCO ratio also demonstrates good predictive performance: FVC/DLCO 0.44 can effectively identify PH [57], and ratio > 0.41 [58] significantly reduces 5-year survival rate in COPD patients. Furthermore, DLCO reduction better reflects hemodynamic abnormalities than ventilation parameters [59]. Research shows that each 1% predicted decrease in DLCO increases mortality risk by 4% in COPD-PH patients; when <32% predicted, 5-year survival rate drops to 13% [42]. In PH associated with chronic lung disease [13], each 10% decrease in DLCO increases mortality risk by 31%, independent of other clinical variables. A prospective multicenter study showed that DLCO decline was more significant in severe COPD-PH patients, accompanied by obvious hypoxemia and elevated pulmonary artery pressure, with average survival of only 15 months, indicating DLCO' s important value for COPD-PH phenotype identification and prognosis assessment [60]. Therefore, DLCO in COPD-PH patients not only has sensitive screening and classification capabilities but also accurately predicts severe PH and long-term mortality risk, suggesting its potential role in comorbidity management and early screening.

In COPD patients with HF, DLCO decline is significantly associated with increased arterial stiffness and reduced exercise capacity [61-62]. Although its predictive power for cardiopulmonary events or death is limited [62], DLCO' s predictive value for exercise-induced hypoxemia is more prominent in heart failure with preserved ejection fraction (HFpEF) patients. FERMOYLE et al. [62] found that DLCO reduction reflects alveolar-capillary barrier dysfunction during exercise, representing the main mechanism of exercise hypoxemia in HFpEF patients. Therefore, in COPD with HF, particularly HFpEF, DLCO has limited death prediction value but serves as an important predictor of exercise hypoxemia with unique value in identifying pulmonary vascular dysfunction.

In mild COPD patients with non-small cell lung cancer (NSCLC), DLCO is also important for postoperative risk assessment. Preoperative DLCO <80% predicted and DLCO/VA (diffusing capacity per alveolar volume) <80% predicted can independently predict postoperative pulmonary complications, with DLCO/VA showing the strongest predictive power. Additionally, incorporating DLCO into the COPD-lung cancer screening scoring system [63] demonstrates good discriminatory ability. DLCO <60% can replace CT-detected emphysema, correlating highly with quantitative CT emphysema, independently predicting lung cancer diagnosis and death risk, and increasing death risk 2.4-fold in high-risk groups [64]. Therefore, DLCO can effectively predict postoperative complications in COPD-lung cancer patients and shows important clinical value in lung cancer screening system applications.

4. Limitations and Future Prospects

4.1 Limitations Despite DLCO' s important clinical value in COPD management, its widespread application faces numerous challenges. First, equipment availability is limited. Currently, DLCO measurement equipment is expensive and requires complex technical operation, restricting its promotion and application in primary healthcare institutions. However, with continuous development of portable pulmonary function devices, China has issued relevant expert consensus [65], providing guidance on principles, quality control, and clinical application of portable spirometers. However, DLCO measurement has not yet been implemented. With technological advances, the newly launched MiniBox+™ portable device [66] can accurately measure DLCO with advantages of simple operation, low failure rate, and lower cost, making it particularly suitable for primary care and mobile testing scenarios.

Second, significant equipment variability affects comparability of DLCO measurement results, particularly between different regions and institutions. DLCO measurements are susceptible to multiple factors including age, height, hemoglobin concentration, and ambient pressure, requiring multidimensional parameter integration for clinical interpretation.

4.2 Future Prospects With rapid development of artificial intelligence (AI) and machine learning (ML) technologies, pulmonary function test analysis has achieved new breakthroughs. ML models can automate processing of continuous data and graphics from pulmonary function tests (e.g., DLCO curves), effectively reducing subjective differences in manual interpretation and discovering potential physiological markers. Combined with patient clinical data and dynamic breathing patterns [67], ML can also construct precise COPD risk prediction models, enabling early warning and personalized treatment plan formulation to effectively reduce disease exacerbation incidence.

AI-DLCO integration applications extend beyond COPD research, with diagnostic value similarly important in other diseases. For example, AI can identify imaging features of asbestosis through chest CT analysis, and combined with DLCO, significantly improves diagnostic efficacy (AUC up to 0.95) [68], demonstrating complementary value of structural imaging and functional data. Additionally, AI deep learning can automatically extract fibrosis extent from CT images and combine with DLCO percent predicted (DLCO%pred) and other pulmonary function parameters [69] to construct mortality risk prediction models for idiopathic pulmonary fibrosis patients, effectively quantifying disease severity. Latest research shows [70] that AI-quantified imaging metrics significantly correlate with dynamic changes in DLCO and other pulmonary function parameters, providing new objective basis for disease progression monitoring and prognosis evaluation in systemic sclerosis-associated interstitial lung disease.

Studies show that emphysema-predominant and bronchitis-predominant COPD phenotypes differ in DLCO and CT parameters, suggesting its value in clinical classification and differential diagnosis [71-72]. NI et al. [72] indicated that DLCO%pred in emphysema-predominant COPD patients is significantly lower than in non-emphysema patients, serving as an important physiological indicator to distinguish emphysema-predominant from chronic bronchitis-predominant COPD.

In recent years, imaging technology innovations have provided new pathways for DLCO assessment. Hyperpolarised xenon-129 magnetic resonance imaging (HXeMRI) [73], as an emerging imaging technology, shows high correlation between its gas transfer capacity to red blood cells and DLCO%pred, becoming an important imaging indicator for assessing pulmonary diffusion function. Particularly in COPD patients with reduced DLCO%pred but mild emphysema, HXeMRI can effectively identify different pathological types, demonstrating its potential in early classification and functional impairment detection.

In summary, future DLCO clinical applications will gradually shift from traditional functional testing to comprehensive assessment integrating structural and functional data. DLCO will more accurately reflect pathological changes in COPD and its comorbidities, providing powerful support for early identification, disease assessment, and prognosis prediction. These technological breakthroughs will greatly enhance DLCO' s clinical application value and promote further development of COPD management.

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