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REVIEW

Prognostic Value of Biomarkers in Chronic Obstructive Pulmonary Disease: A Comprehensive Review

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Abstract: Chronic Obstructive Pulmonary Disease (COPD) is a prevalent chronic respiratory disorder characterized by airway inflammation and irreversible airflow limitation. Its marked heterogeneity and complexity pose significant challenges to traditional clinical assessments in terms of prognostic prediction and personalized management. In recent years, the exploration of biomarkers has opened new avenues for the precise evaluation of COPD, particularly through multi-biomarker prediction models and integrative multimodal data strategies, which have substantially improved the accuracy and reliability of prognostic assessments. This review summarizes the key biomarkers associated with COPD prognosis, systematically discusses the practical applications and future potential of combined predictive models and multimodal data integration, and evaluates their translational value in clinical practice. As a narrative review, this study aims to provide a scientific foundation for the precision management of patients with COPD.

Keywords: pulmonary disease, chronic obstructive, biomarkers, prognosis prediction

Introduction

COPD is a chronic inflammatory disease caused by prolonged exposure to toxic particles or gases, leading to damage of the small airways and lung parenchyma, and is associated with high morbidity and mortality rates.[1] According to the World Health Organization (WHO), COPD has become the fourth leading cause of death globally.[2] Its clinical heterogeneity and complexity continue to pose major challenges for long-term management and prognostic prediction, particularly in resource-limited settings. The *Medium- and Long-term Plan for the Prevention and Treatment of Chronic Diseases in China (2017–2025)*, issued by the National Health Commission, clearly states that by 2025, the standardized management rate of COPD patients should exceed 60%.[3] Furthermore, in 2024, China officially integrated COPD management into the national public health service system, highlighting the growing importance of this disease.

Studies have shown that a primary cause of in-hospital death among COPD patients may be the lack of timely and individualized monitoring, and that 5.2% of such deaths are potentially preventable.[4] In recent years, several biomarkers —such as eosinophil count (EOS),[5] chitinase-3-like protein 1 (CHI3L1),[4] and fibrinogen (FIB)[6]—have been identified as closely associated with COPD outcomes. An increasing number of biomarkers have drawn attention for their potential to reduce disease heterogeneity and enable precision treatment. In particular, when combined with clinical and radiologic parameters, their prognostic performance significantly outperforms that of single biomarkers.[6–8]

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Despite the growing body of research on COPD biomarkers, their discovery and clinical implementation still face substantial challenges. Most biomarkers remain in the exploratory phase and have yet to be widely adopted in clinical practice. As a narrative review, this review summarizes key prognostic biomarkers for COPD, explores the application of multi-biomarker predictive models and multimodal data integration strategies, and evaluates their potential value in prognosis prediction and clinical translation, with the aim of providing scientific guidance for the precision management of COPD patients.

Prognostic Evaluation of COPD Using Biomarkers

Systemic Inflammatory Biomarkers

C-Reactive Protein

C-reactive protein (CRP) is a pentameric protein synthesized in the liver, regulated by cytokines such as interleukins and tumor necrosis factor during the nonspecific immune response. It serves as a sensitive marker of inflammatory diseases and shows significantly elevated levels during acute exacerbations of COPD (AECOPD). A meta-analysis demonstrated that the mean CRP levels in patients with bacterial AECOPD were significantly higher than those in patients with non-bacterial AECOPD, with moderate quality of evidence.[9] Moreover, a recent case-control study found that patients with CRP levels ≥5 mg/L had a 1.6-fold increased risk of experiencing AECOPD compared to those with lower CRP levels, and this association remained significant after adjusting for potential confounding factors.[10]

Procalcitonin

Procalcitonin (PCT) is a precursor protein initially synthesized by thyroid C cells and then cleaved by endopeptidase to be converted into procalcitonin. It is mainly responsible for processes such as serum calcium regulation. The level of PCT in the peripheral blood of healthy individuals is generally lower than 0.05ng/mL, and its level is significantly increased in bacterial infections, especially sepsis.[11] A study of 204 inpatients with AECOPD showed that the PCT level of patients with bacterial infection was higher than that of the non-bacterial infection group, and the optimal cut-off value of PCT was established as 0.08 ng/mL, with a sensitivity of 81% and a specificity of 67% (AUC=0.794).[12] Furthermore, the study found that the average PCT level of patients with AECOPD (0.06 ± 0.07 ng/mL) was significantly higher than that of patients with stable COPD (0.04 ± 0.02 ng/mL), $P < 0.05$. The neutrophil levels of AECOPD patients involved in this study were much higher than those of patients with stable COPD (81.11 ± 14.90 vs 61.80 ± 9.95), suggesting bacterial infection.[10] This further proves the important role of PCT in differentiating acute exacerbation of COPD, which is often a bacterial infection process.

Interleukin-6

Interleukin-6 (IL-6) is a cytokine produced by various lymphoid and non-lymphoid cells. It regulates inflammatory and immune responses by activating Janus kinase (JAK), which in turn triggers downstream signaling pathways such as JAK-STAT, MAPK, and PI3K-AKT.[13] IL-6 has been associated with lung function decline and tissue remodeling in COPD. It has been shown to correlate significantly with disease severity, frequency of acute exacerbations, and mortality in long-term follow-up studies of COPD patients.[9] A study by Bradford et al found that IL-6 levels were positively correlated with emphysema progression and the rate of FEV_1 decline in COPD patients ($P < 0.05$).[14] IL-6 also inhibits lipoprotein lipase activity, and elevated IL-6 levels have been linked to malnutrition and reduced muscle strength in COPD patients ($P = 0.002$).[15]

Tumor Necrosis Factor-Alpha

Tumor necrosis factor-alpha (TNF-α) is a multifunctional cytokine primarily synthesized by monocytes. It activates neutrophils and monocytes to produce pro-inflammatory mediators and plays a critical role in airway remodeling and lung function decline in patients with COPD. Meta-analyses have shown that TNF-α levels are significantly elevated in patients with AECOPD, particularly in the presence of bacterial infections, making it an important marker for assessing disease severity in AECOPD.[9] Compared to healthy controls, TNF-α levels were significantly elevated in both exacerbation and stable phases of COPD (11.43 ± 11.91 vs 5.99 ± 5.29, $P = 0.034$; 14.87 ± 36.03 vs 5.99 ± 5.29, $P = 0.033$).[16]

Transforming Growth Factor-Beta

Transforming growth factor-beta (TGF-β) plays a pivotal role in airway remodeling and fibrosis by phosphorylating downstream Smad2 and Smad3, thereby activating the Smad signaling pathway. This cascade influences apoptosis, extracellular matrix (ECM) deposition, and epithelial-mesenchymal transition (EMT). Studies have shown that TGF-β can promote the EMT process by activating gene expression via the Smad pathway, thus enhancing fibrosis—a phenomenon particularly evident in the airways of COPD patients and recognized as one of the main contributors to airway remodeling and alveolar wall destruction.[17] In addition, while TGF-β facilitates tissue repair in the early stages of disease, chronic exposure to environmental factors such as cigarette smoke may dysregulate TGF-β signaling, leading to aberrant tissue remodeling and accelerating COPD progression. This highlights the dual role of TGF-β in the development of smoking-related COPD.[18]

Inflammatory Cell-Associated Biomarkers

Eosinophil Count

Eosinophils are innate immune cells derived from hematopoietic stem cells in the bone marrow. Under inflammatory stimulation, they infiltrate the airways and promote the sustained release of cytokines and cytotoxic substances, contributing to persistent inflammation and tissue damage. Their count may hold significant clinical value in the progression of COPD. Bartziokas et al found that COPD patients blood eosinophil counts (EOS) below 150 k/μL had more severe conditions at admission and significantly longer hospital stays ($P<0.001$), and this threshold could independently predict the need for Non-invasive Ventilation (NIV) during hospitalization.[8] Furthermore, Yeon-Mok Oh et al found that patients with EOS%<2% and absolute value <100/μL had longer hospital stays, increased mechanical ventilation rates, inflammatory indicators, and the combined rate of pulmonary hypertension (all $P<0.05$).[5] However, Vedel-Krogh et al[19] found that the risk of severe acute exacerbation in COPD patients with EOS≥0.34×10^9/L increased by 1.76 times (95%, 1.56–1.99). High EOS level was an independent predictor of future disease deterioration (adjusted OR=1.54, 95% CI 1.22–1.94).[20] The cohort study by Singh et al[21] demonstrated that 37% of COPD patients with persistent EOS≥2% had increased responsiveness to corticosteroids. Eosinophil count greater than $0{\cdot}10 \times 10^9$ cells /L can be used as an independent predictor of the response to disease deterioration alleviated by budesonide - formoterol treatment (p=0.013), and as a feature for predicting the clinical response of COPD to ICS to guide medication.[22]

This apparent contradiction reflects divergent pathophysiological mechanisms in COPD endotypes: The low-EOS phenotype is driven by neutrophil-mediated irreversible parenchymal destruction (eg, emphysematous remodeling/pulmonary fibrosis), correlating with poor hospitalization outcomes. Conversely, the high-EOS phenotype demonstrates corticosteroid-responsive airway inflammation mediated, exhibiting higher exacerbation susceptibility but favorable ICS responsiveness. Consequently, therapeutic strategies should be phenotype-specific: low EOS indicates the need to pay attention to the management of structural complications (such as anti-fibrosis), while high EOS is suitable for glucocorticoid treatment.

Neutrophil-to-Lymphocyte Ratio (NLR)

The neutrophil-to-lymphocyte ratio (NLR) is an indicator of immune dysregulation under stress conditions and plays a critical role in evaluating inflammatory status and predicting disease prognosis. A study by Eraslan et al found that NLR was significantly associated with clinical outcomes in COPD patients, including length of hospital stay, duration of mechanical ventilation, and ICU stay.[23] Research has shown that an NLR above the threshold of 7.97 is strongly correlated with increased nutritional risk and disease severity ($P < 0.001$).[24] A case-control study involving 533 AECOPD patients demonstrated that a high NLR value (≥5.5) had good sensitivity and specificity for predicting 28-day mortality (AUC = 0.778), suggesting that NLR may serve as an effective prognostic marker in COPD.[25]

Platelet-to-Lymphocyte Ratio

The platelet-to-lymphocyte ratio (PLR) is considered a novel marker of systemic inflammatory diseases. During stress, increased cortisol secretion leads to a transient rise in platelet count and a temporary decrease in lymphocyte count; thus, changes in PLR can comprehensively reflect the activation of the inflammatory response. Studies have shown that PLR levels are significantly elevated during AECOPD and positively correlate with disease severity and length of hospital stay ($P = 0.009$).[25] Both stable and

exacerbation-phase COPD patients exhibit significantly higher PLR values compared to non-COPD individuals (WMD: 59.52, 95% CI: 29.59–89.44; WMD: 46.03, 95% CI: 7.70–84.35).[26] Logistic regression analysis has identified PLR, NLR, and APACHE II scores as independent prognostic risk factors in COPD patients with respiratory failure.[27] Another case-control study reported that PLR in ICU-admitted COPD patients was significantly associated with hospital stay duration, mechanical ventilation time, and ICU length of stay, and showed strong predictive value for 30-day mortality ($P < 0.001$).[23]

Monocyte-to-Lymphocyte Ratio and Lymphocyte-to-Monocyte Ratio

The monocyte-to-lymphocyte ratio (MLR) is a composite indicator that has demonstrated significant value in predicting systemic diseases such as cancer and immune disorders, offering a more dynamic reflection of inflammatory status than single-cell counts. A study by Long et al found that MLR levels were significantly higher in the AECOPD group compared to healthy controls.[28] Moreover, Hosseninia et al showed through Kaplan–Meier survival analysis that higher MLR values in COPD patients were associated with lower survival rates (HR: 2.022, 95% CI: 1.030–3.968),[29] suggesting the potential of MLR in staging and prognostic assessment.

The lymphocyte-to-monocyte ratio (LMR) is considered an important parameter for nutritional evaluation. In COPD patients, a reduced LMR is generally indicative of an increased risk of malnutrition. Studies have shown that when LMR exceeds the critical threshold of 2.60, it is closely associated with immune function, disease severity, and prognosis.[24]

AISI, SII, and SIRI Indices

The Aggregate Index of Systemic Inflammation (AISI; AISI = neutrophils × platelets × monocytes / lymphocytes) is a novel marker that provides a comprehensive evaluation of systemic inflammatory status by integrating both inflammatory and immune mechanisms. Studies have shown that in COPD patients with concurrent COVID-19 infection, higher AISI levels at admission are associated with significantly lower survival rates (HR: 2.010, 95% CI: 1.048–3.855),[29] indicating its important role in predicting mortality risk in this subgroup.

The Systemic Immune Inflammation Index (SII; SII = neutrophil count × platelet count × monocyte count / lymphocyte count) is an emerging biomarker for assessing airway immune-inflammatory responses in COPD. A cross-sectional study involving 16,636 participants revealed that higher SII levels were positively associated with both COPD risk and all-cause mortality, and that SII outperformed traditional markers such as NLR and PLR in predicting COPD risk.[30] Furthermore, SII was inversely correlated with lung function, further supporting its value in evaluating COPD severity.[31]

The Systemic Inflammatory Response Index (SIRI; SIRI = monocytes × neutrophils / lymphocytes) reflects the systemic inflammatory burden during COPD progression. SIRI levels may increase as a result of reactive oxygen species (ROS)-induced activation of inflammatory pathways and recruitment of immune cells. Studies have found that SIRI has strong predictive power for COPD exacerbation, second only to PLR.[32] Additionally, among COPD patients with COVID-19 co-infection, those with higher SIRI values faced a significantly increased risk of mortality ($P < 0.05$).[29]

HALP Score

The Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) score is an integrated marker reflecting systemic inflammation and nutritional status, which was defined as follow: HALP = Hemoglobin (g/L) × Albumin (g/L) × Lymphocytes (/L) / Platelets (/L). It has been widely used in the prognosis and prediction of various cancers since it was proposed in 2015,[33] and recent studies have highlighted its relevance to the prognosis of COPD patients as well. A retrospective cohort study by Han et al found that in AECOPD patients admitted to the ICU through the emergency department—particularly those who were obese and had lower APACHE II scores—a low HALP score (HALP<18.5) was significantly associated with an increased risk of ICU mortality (HR: 1.69, 95% CI: 1.14–2.53), after the combined APACHE II score, the AUC rose from 0.72 to 0.88.[34] Another study showed that the HALP score demonstrated high predictive accuracy for ICU outcomes in AECOPD patients with respiratory failure (AUC = 0.994), the HALP score of the 18 death cases (31.42 ± 4.67) was much lower than that of the 50 control cases (67.72 ± 12.39) ($P < 0.05$), supporting its utility in guiding clinical assessment of treatment efficacy.[35] The calculation of HALP may be recommended as a new simple method and supplement to predict the survival outcome of patients with AECOPD.

Metabolism-Related Biomarkers

Creatinine, Cystatin C, and the Cr/CysC Ratio

Creatinine (Cr) is a metabolic byproduct of muscle activity and is not only closely related to renal function but also significantly associated with sarcopenia. Afzal et al suggested that muscle mass may be a stronger predictor of mortality in COPD patients than body mass index (BMI), and that pre-admission Cr levels could predict 1-year post-admission mortality risk.[36]

Cystatin C (CysC), a cysteine protease inhibitor expressed in all nucleated cells, serves as a sensitive marker of renal function. Elevated levels of CysC (≥1.59 mg/L) have been significantly associated with all-cause mortality and increased cardiovascular risk in COPD patients.[37]

The Cr/CysC ratio is closely linked to muscle mass. COPD patients with a low Cr/CysC ratio (<0.71) tend to have reduced handgrip strength, poorer lung function, and a higher frequency of acute exacerbations. Additionally, they exhibit significantly higher overall mortality compared to those with higher ratios.[38] A low Cr/CysC ratio may indicate dyspnea and functional impairment in COPD patients and can serve as an effective marker for identifying high-risk individuals during exacerbation episodes.[39]

Chloride Ion

Chloride ion (Cl^-) is the second most abundant electrolyte in serum and plays a critical role in maintaining electrolyte and acid–base balance. In recent years, its potential impact on COPD prognosis has received increasing attention. One study found that low Cl^- levels were significantly associated with disease severity in AECOPD patients, and Cl^- was identified as an independent predictor of COPD prognosis ($P = 0.002$).[40]

Furthermore, a retrospective cohort study based on the MIMIC-IV database revealed that critically ill COPD patients with higher Cl^- levels had significantly lower all-cause mortality at both 90 and 365 days ($P < 0.05$). Further analysis indicated an L-shaped relationship between Cl^- levels and mortality risk, suggesting that elevated Cl^- levels may be associated with improved long-term survival in COPD patients.[41]

Cholinesterase

Cholinesterase (ChE) primarily functions to hydrolyze acetylcholine in the body and also plays a role in chronic airway inflammation and oxidative/antioxidant imbalance. Its reduction often parallels hepatic dysfunction. Retrospective studies have identified low serum ChE levels (≤4323 U/L) as an independent risk factor for in-hospital mortality in COPD patients.[42]

ChE levels are closely associated with clinical outcomes in AECOPD patients. Specifically, a ChE level ≤4116 U/L significantly increases the risk of requiring non-invasive ventilation ($P = 0.002$).[43] Moreover, further research has shown that low ChE levels are significantly associated with hypercapnia, hypoxemia, and prolonged hospital stays in AECOPD patients, highlighting its importance in the clinical assessment of disease severity.[43]

Lung Injury and Tissue Repair-Related Proteins

Tyrosine-Lysine-Leucine-40

Chitinase-3-like protein 1 (CHI3L1), also known as Tyrosine-Lysine-Leucine-40 (YKL-40), is a member of the glycoside hydrolase family 18. It plays a role in various biological processes—including oxidative stress regulation, apoptosis, and Th1/Th2 inflammatory balance—and has emerged as an important biomarker in the diagnosis and prognostic assessment of multiple inflammatory diseases. A study by Holmgaard et al found that elevated plasma levels of YKL-40 were significantly associated with increased mortality risk (HR: 1.38, 95% CI: 1.11–1.72, $P = 0.004$), identifying it as an independent predictor of mortality in COPD patients.[7]

In addition, YKL-40 has been shown to correlate significantly with hypoxemia and disease severity in COPD ($P = 0.005$).[44] Serum YKL-40 levels in patients with severe COPD were positively associated with leukocyte count and NLR, suggesting a key role for YKL-40 in COPD-related inflammation and immune dysregulation.[45]

Pulmonary Surfactant-Associated Protein D and Pulmonary Surfactant-Associated Protein A

Pulmonary surfactant-associated protein D (SP-D) is a pattern recognition receptor primarily secreted by alveolar type II epithelial cells. It exhibits immunomodulatory and antiviral properties. Surfactant protein A (SP-A), a hydrophilic member of the C-type lectin family, also contributes to innate immune defense in the alveoli. Studies have shown that

serum SP-D levels in COPD patients are closely associated with disease severity. During acute exacerbations, elevated SP-D levels are negatively correlated with pulmonary function parameters (FVC, FEV_1) and positively correlated with hospital stay duration, complications, and the need for mechanical ventilation.[46]

Similarly, serum SP-A levels are significantly associated with COPD staging ($P < 0.001$), suggesting that SP-A may reflect disease progression in COPD patients.[47]

Epigenetic-Related Biomarkers

Long Noncoding RNA

Long noncoding RNAs (lncRNAs) are involved in the regulation of chromatin structure, transcription, and post-transcriptional processes. Dysregulation of their expression is closely associated with the onset and progression of COPD, making them key prognostic and diagnostic biomarkers. Studies have shown that elevated expression of lncRNAs such as MALAT1 and HOTAIR in COPD patients is associated with poorer outcomes, as these molecules contribute to disease pathogenesis by modulating inflammatory responses, oxidative stress, and airway remodeling.[48]

Research by Tokgun et al and Zhang et al further demonstrated that MALAT1, HOTAIR, and GAS5—owing to their tissue-specific expression and stability in biological fluids—hold significant potential for predicting disease progression and prognosis in COPD.[49,50]

Circular RNA

Circular RNAs (circRNAs) are a class of noncoding RNAs characterized by a covalently closed loop structure formed through back-splicing of precursor mRNA. They are involved in the regulation of NLRP3 inflammasome activation, apoptosis, and oxidative stress. Studies have demonstrated that circRNAs are abnormally expressed in the blood and lung tissues of COPD patients, and are closely associated with inflammatory responses and airway remodeling.[51]

Chen et al found that circRNA0001859 was downregulated in both COPD and AECOPD patients, with areas under the ROC curve (AUC) of 0.7433 and 0.8717, respectively, indicating its strong diagnostic potential.[52] Moreover, recent research has shown that circTMEM30A is most highly expressed in patients with COPD complicated by lung cancer, suggesting it may serve as a potential predictive biomarker for the coexistence of COPD and lung cancer.[53]

MicroRNA

MicroRNAs (miRNAs) are a class of endogenous small noncoding RNA molecules. Their dysregulation contributes to COPD pathogenesis by modulating key signaling pathways, including Notch, NF-κB, and Wnt/β-catenin.[54] Chen et al found that miR-146a and miR-146b were significantly downregulated in AECOPD patients and exhibited strong diagnostic potential in predicting the risk of AECOPD in healthy individuals, with AUCs of 0.702 and 0.715, respectively.[55]

MiR-132 is upregulated in the peripheral blood of COPD patients and is negatively correlated with the FEV_1/FVC ratio. It promotes the release of inflammatory cytokines by suppressing the expression of SOCS5.[56] Moreover, extracellular vesicles (EVs), including exosomes, participate in intercellular communication by delivering proteins, lipids, and miRNAs. Notably, exosomal miR-21 levels are negatively correlated with lung function (FEV_1/FVC%) in COPD patients, highlighting the potential of exosomal miRNAs as biomarkers for COPD.[57]

The Role of Combined Biomarker Prediction in COPD Prognosis

COPD is a complex chronic inflammatory airway disease resulting from multifactorial and multistep interactions. These factors are interrelated, making it difficult for a single parameter to achieve optimal predictive outcomes. A combination of multiple biomarkers, or their integration with clinical and imaging indicators, may provide superior prognostic value compared to the use of individual biomarkers alone.

Although single inflammatory markers have limited predictive power, indicators such as C-reactive protein (CRP), fibrinogen (FIB), and white blood cell count (WBC) are often used together for COPD prognosis. One study proposed that CRP, FIB, and WBC could be utilized as a composite tool to assess AECOPD risk.[6] Agustí et al found that patients with persistent elevation in at least two inflammatory biomarkers (WBC, CRP, IL-6, and TNF-α) had a significantly higher annual rate of AECOPD compared to those without such elevation ($P < 0.001$).[58] Similarly, Thomsen et al observed that COPD

patients with simultaneous elevations in three biomarkers (CRP, FIB, and WBC) had nearly threefold higher absolute risk of frequent exacerbations over five years compared to those with normal levels (62% vs 24%).[59] The combined use of TNF-α with other inflammatory markers has also been shown to significantly enhance prognostic accuracy. For instance, co-detection of TNF-α and IL-6 significantly improves sensitivity and specificity in predicting exacerbation risk, enabling better identification of high-risk patients and refinement of personalized treatment strategies.[60] The addition of other inflammatory markers such as IL-8 and FIB may further enhance the accuracy of risk assessment in COPD patients.[61] TGF-β, beyond its role as a profibrotic factor, interacts synergistically with other pro-inflammatory cytokines to influence COPD prognosis. One study showed that the combination of TGF-β and IL-6 enhanced the activation of inflammatory signaling pathways and promoted EMT via Smad signaling, playing a key role in airway remodeling in COPD patients.[17] Additionally, TNF-α may accelerate ECM deposition, thereby intensifying fibrosis and airway remodeling. The combined assessment of TGF-β and TNF-α has been shown to improve the ability to predict COPD progression.[62] During AECOPD episodes, PLR combined with other inflammatory markers also demonstrates strong predictive efficacy. For example, while the AUC of PLR alone in predicting 28-day mortality in AECOPD is 0.75, it increases to 0.857 when combined with NLR and CRP, significantly enhancing predictive power. Further integration with APACHE II scores and CRP improves the prediction of hospital stay and mortality.[25,63] The Cr/CysC ratio, as a marker for sarcopenia in COPD patients, offers a more comprehensive prognostic perspective when used alongside other clinical indicators. Hirai et al reported that patients with a low Cr/CysC ratio (<0.71) were at higher risk of acute exacerbation. When combined with pulmonary function indices (FEV_1, FVC) and BMI, it provided more accurate prognostic evaluation.[38]

The Role of Multimodal Evaluation Strategies in COPD Prognosis

With continuous advancements in biomedical technology, researchers are now able to acquire multidimensional data across various modalities for a single disease, including mRNA expression, DNA methylation, microRNA (miRNA) expression, physiological and biochemical data, computed tomography (CT) imaging, and whole-slide imaging (WSI) data. While unimodal data capture only partial aspects of biological complexity, the integration of multimodal data enables a more comprehensive understanding of underlying biological processes. As a highly complex and information-rich system, the human body serves as a natural database encompassing diverse dimensions of medical data. Multimodal learning, which mimics the brain's ability to process multisource inputs and make rational decisions, has been widely demonstrated to perform at levels comparable to—or even exceeding—those of human experts in clinical decision support systems, offering critical technological support for modern medicine.[64] Liu Zhuo et al developed an auxiliary diagnostic model for infectious respiratory diseases based on multimodal deep feature fusion. The model integrates high-throughput genomic data, clinical manifestations, laboratory test results, and imaging data. By designing an optimized algorithm to address data imbalance and missing values, and using unsupervised learning to extract shared features across modalities, the system combines a knowledge graph to enhance semantic correlations within the model. This approach achieves end-to-end disease prediction, offering a novel method for the precise diagnosis of infectious respiratory diseases.[64] Xie et al proposed a Transformer-based multimodal data fusion framework that integrates graph neural networks and 3D convolutional neural networks to process physiological-biochemical data and lung CT images. By employing low-rank multimodal fusion and cross-modal Transformer architectures, the model enhances complementarity across modalities. It demonstrated superior performance in COPD classification tasks and identified key indicators such as BMI, APTT, body weight, and albumin, thereby providing a new direction for multimodal data processing and disease classification.[65] Kumar et al designed an innovative multimodal framework for early diagnosis and classification of COPD using CT scan images combined with lung sound and cough samples. The framework extracts texture, histogram intensity, chromaticity, MFCC features, and Gaussian scale-space features from both CT and audio samples. Through unsupervised learning, it selects discriminative features, and applies a customized ensemble learning method for early COPD classification and severity assessment. Experimental results showed high accuracy for the multimodal fusion model (97.50%), the CT-based model (98%), and the cough-sample model (95.30%). Compared with existing methods, this framework demonstrated significant advantages in early diagnostic accuracy.[66]

Table 1 Summary of Prognostic Biomarkers Related to COPD

Biomarkers	Acute Exacerbation	Severity	Length of Hospital Stay	ICU Stay Duration	Ventilation Duration	Bacterial Infection	Respiratory Failure	Hypoxemia	Mortality Rate	Pulmonary Function	Emphysema	Malnutrition	Muscle Weakness
Systemic Inflammatory Biomarkers													
CRP	√					√							
PCT		√				√							
IL-6	√	√							√	√	√	√	√
TNF-α	√					√							
TGF-β	Dual effect: early repair, long-term pathological remodeling												
Inflammatory Cell-Associated Biomarkers													
EOS		√	√		√								
NLR		√	√	√	√				√			√	
PLR		√	√	√	√		√		√				
MLR	√								√				
LMR		√										√	
AISI									√				
SII									√	√			
SIRI	√								√				
HALP							√		√				
Metabolism-Related Biomarkers													
Cr									√				
CysC									√				
Cr/CysC	√								√	√			√
Cl-		√							√				
ChE			√		√			√	√				
Lung Injury and Tissue Repair-Related Proteins													
YKL-40		√						√	√				
SP-D		√	√		√					√			
Epigenetic-Related Biomarkers													
LncRNA	**Inflammation, oxidative stress and airway remodeling regulation**												
CircRNA	√												
MiRNA	√									√			

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Conclusion

This review summarizes key prognostic biomarkers for COPD (Table 1), including inflammatory markers, inflammatory cell-associated biomarkers, metabolic indicators, proteins related to lung injury and tissue repair, and epigenetic biomarkers. Their potential value in predicting the disease course of COPD has been thoroughly explored. Although the predictive ability of individual biomarkers is limited, combining multiple biomarkers—or integrating them with clinical and imaging data—can substantially improve the accuracy of prognostic assessments. Such multimodal data integration strategies pave the way for precision evaluation and personalized management of COPD.

GOLD guide has been proposed, A blood eosinophil count (EOS) of ≥300 cells/μL can be regarded as part of guiding the medication management of patients with AECOPD using inhaled glucocorticoids (ICS) combined with long-acting bronchodilators (LABA/LAMA). The "Chinese Guidelines for Primary Care, Diagnosis and Management of Chronic Obstructive Pulmonary Disease (2024)" also mentions that biomarkers play a significant role in the management of COPD, especially in the diagnosis and prognosis assessment during the acute exacerbation period. Biomarkers such as CRP and procalcitonin (PCT) can be used to assist in the examination and assessment of inflammation levels. Nonetheless, current research and clinical application of COPD biomarkers still face several challenges. Most of COPD biomarkers are based only on existing studies and have not been verified in large-scale multicenter studies, and issues related to data standardization and clinical translation remain to be addressed. Future research should focus on the following areas: (1) Strengthening clinical validation to ensure biomarker stability and reproducibility; (2) Exploring novel biomarkers and their synergistic potential with existing clinical indicators to enhance early diagnosis, risk stratification, and treatment response evaluation; (3) Developing multimodal assessment strategies that integrate genomics, imaging, and clinical data to further refine prognostic precision in COPD.

In conclusion, biomarker research in COPD not only deepens our understanding of disease mechanisms but also offers practical technological support for precision medicine. By optimizing biomarker selection and multimodal integration approaches, there is promising potential to improve prognostic evaluation frameworks and advance the development of personalized care in COPD management.

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Disclosure

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