Omics methods predict the prognosis and treatment efficacy of chronic obstructive pulmonary disease

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To the Editor: Chronic obstructive pulmonary disease (COPD) is a condition that severely endangers human health. In 2018, Wang *et al*[1] reported that there are approximately 100 million patients with COPD in China, with a 13.7% prevalence in people aged over 40 years. The disease severity, frequency of exacerbations, and comorbidities, which are commonly (30–57%) observed in patients with COPD, are the three most crucial elements affecting the economic and societal consequences of COPD.[2] Hospitalizations for exacerbations are the main contributors to health care expenses. To reduce the clinical and financial burden of COPD, interventions are needed to slow the disease course, avoid exacerbations, and reduce comorbidities, such as approaches for improving the prognosis and treatment efficacy in COPD. Advances in high-throughput omics technology have revolutionized disease research. We gathered data regarding omics methods in the field of COPD research. Genomics, transcriptomics, single-cell transcriptome analysis, proteomics, metabolomics, microbiomics, radiomics, and pharmacogenomics studies were obtained from the PubMed database. Our findings revealed the factors related to COPD prognosis and treatment efficacy by using omics data with predictive potential [Supplementary Figure 1, http://links.lww.com/CM9/B913]. Omics may constitute a powerful tool for monitoring COPD prognosis, providing hope for future individualized treatment.

Omics technology innovations, along with biomedical advances and the emergence of techniques for large data analysis, have brought medical care closer to personalized medicine using genetic and molecular data. Genomics technology is widely used in biology and medicine. Single-cell transcriptomics reveals the molecular basis of single-cell behavior. Proteomics studies the composition and activity of all cellular proteins. Current proteomics applications include mass spectrometry and aptamer methods. Metabolomics, the omics closest to biological phenotypes, is used to analyze overall biological/cellular metabolites. Microbiomics systematically studies all microorganisms in a specific environment and their interactions. Radiomics involves extraction of quantitative metrics, known as radiomic features, which capture tissue and lesion characteristics such as heterogeneity and shape. Pharmacogenetics is widely used to examine how genetic variations across the genome and population affect drug responsiveness.

COPD is complex, multifactorial, and influenced by genetic and environmental variables. The first identified genetic determinant of COPD was severe alpha-1 antitrypsin *(AAT)* deficiency, which remains the most well-established genetic COPD risk factor and the only genetic subtype with a specific therapy.[3] This finding revealed a correlation between genes and COPD pathogenesis, providing theoretical support for genomics-based prediction of COPD prognosis. To date, studies of COPD susceptibility genes remain at an early stage, with further research needed to confirm a causative link.

The literature on genomics-based prediction of COPD prognosis was summarized according to the three observational outcomes in Supplementary Table 1, http://links.lww.com/CM9/B913. The first category (group A) was as follows: Acute exacerbations of chronic obstructive pulmonary disease (AECOPD)–The prognosis is poor if these genes in Supplementary Table 1 (http://links.lww.com/CM9/B913) are present since they may predict future AECOPD. Polymorphism, which protects against frequent AECOPD, may predict a good COPD prognosis. The second category (group B) was as follows: Severity and decreasing function–COPD severity reflects decreased lung function, including forced expiratory volume in 1 s

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(FEV_1) and forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) ratio, suggesting poor prognosis. Genes associated with COPD severity suggest poor prognosis, whereas genes associated with reduced COPD risk and delayed lung function decline suggest good prognosis. The third category (group C) was as follows: survival or mortality. Mucus hypersecretion correlates with morbidity, frequent exacerbations, and mortality in patients. One mechanism driving mucus hypersecretion in COPD is abnormal DNA methylation of *SPDEF* and *FOXA2*.[4] Accordingly, these factors may indicate a poor prognosis. The literature summary of the relationships between Genomics and COPD indicates the potential for genomics to accurately predict the prognoses of COPD based on the discovery of susceptibility genes, providing strong support for the predictive value of genomics.

High-throughput transcriptome sequencing can provide regulatory information on gene expression. In Supplementary Table 1, http://links.lww.com/CM9/B913, we also summarized three categories of prognosis-related information from the field of COPD transcriptomics. In summary, an intimate association between transcriptomics and COPD has been revealed, along with COPD prognostic prediction capacity. However, studies demonstrating clear causative links are still underway.

Single-cell transcriptomes can reveal the molecular basis of single-cell behavior. A study based on single-cell RNA-sequencing data showed that the severity of airflow limitation and/or prevalence of emphysema was linked with *QKI* and *IGFBP5*, which may predict a poor COPD prognosis [Supplementary Table 1, http://links.lww.com/CM9/B913]. Additionally, this study demonstrated that single-cell sequencing can predict COPD severity. However, the relationships of single-cell transcriptomics data with AECOPD, and mortality remain to be researched.

Proteomics approaches can validate the functions of inflammatory mediators. Inflammatory cytokines and proteases contribute to the onset of COPD. We summarized the relationship between proteomics and various COPD outcomes and studied the prediction power of this relationship while focusing on the application of proteomics in COPD. In Supplementary Table 1, http://links.lww.com/CM9/B913, we summarized the data of COPD-related proteomics studies and highlighted the associations of proteins with AECOPD, COPD severity, and lung function decline. This review mostly presents correlations between proteomics and the outcomes of groups A and B, whereas the associations of proteomics with survival/death still need to be addressed.

Most cellular activities occur at the metabolic level, and thus, changes in metabolites more directly reflect the cellular environment. Among all omics investigations, metabolomics best reflects disease phenotypic information. Several factors derived from metabolomics approaches are associated with AECOPD, severity of COPD, and mortality, and predict poor prognosis. Metabolomics also has the potential to predict COPD survival [Supplementary Table 1, http://links.lww.com/CM9/B913].

The etiology of COPD involves genes and the environment. Although many studies have investigated the influence of smoking and the physicochemical environment, the role of microbes in the occurrence and progression of COPD warrants investigation. We reviewed the research on the relationship between the microbiome and COPD and discovered that microbiomic data can predict acute COPD exacerbations, disease progression, and increased mortality [Supplementary Table 1, http://links.lww.com/CM9/B913]. However, further study of the link between the microbiome and COPD prognosis needs to be performed.

We investigated whether spirometry-based mathematical modeling of airway biomechanical features can reveal the existence and severity of emphysema [Supplementary Table 1, http://links.lww.com/CM9/B913]. Occhipinti *et al*[5] predicted that the existence and severity of emphysema in COPD patients, as measured using CT metrics and CT-based radiomics, can be predicted by mathematical modeling of airway function derived from standard spirometry. The result suggests the possibility of the involvement of radiomics in grading COPD severity. However, whether radiomics techniques can predict COPD prognosis requires further investigation.

Integrated multi-omics can allow diseases to be studied from multiple perspectives. According to research that integrated the microbiome with transcriptomics [Supplementary Table 1, http://links.lww.com/CM9/B913], as COPD severity increases, the airway microbiome composition is progressively altered, which occurs in concert with the downregulation of genes promoting epithelial defense and the upregulation of pro-inflammatory genes associated with inhaled corticosteroids (ICS) use. These multi-omics methods have the potential to predict COPD prognosis, but their ability to predict COPD mortality remains unexplored.

Mining the factors associated with the therapeutic effects of COPD treatments from omics information can promote individualized and effective COPD treatment. COPD treatment typically involves oxygen therapy, systemic corticosteroids, ICS, β2-agonists, anti-cholinergic drugs, and the antioxidant N-acetylcysteine (NAC) [Supplementary Table 2, http://links.lww.com/CM9/B913].

Long-term oxygen therapy (LOTT) decreases mortality in COPD patients with severe hypoxemia. According to Seo *et al*[6] study results, COPD patients with mild hypoxemia did not benefit from oxygen therapy. Variations in the sensitivity to oxygen may be influenced by the genotype or gene expression. In COPD, the responsiveness to long-term oxygen treatment correlates with single nucleotide polymorphisms (SNPs) and *ARSB* expression. The expression quantitative trait loci of *ARSB* SNPs predicted the effectiveness of oxygen therapy. This suggests that *ARSB* SNPs can be used as potential biomarkers to predict the effectiveness of LOTT in individual COPD patients.

Lee *et al*[7] conducted genome-wide association studies (GWAS) to examine the methylation levels of peripheral blood mononuclear cell samples from 24 patients with AECOPD with good or poor response to corticosteroid

therapy and 12 non-COPD controls. They found that *ALOX5AP* CpG sites were specifically associated with a favorable response. Therefore, *ALOX5AP* CpG sites might serve as biomarkers for predicting the efficacy of corticosteroid therapy in AECOPD.

Studies of pharmacogenomics in COPD have mostly focused on *ADRB2*, the gene encoding the β2-adrenergic receptor. The clinical response to β2-agonists may be strongly influenced by β2-adrenergic receptor haplotypes. Researchers found that insensitivity to long-acting β2-agonists may be related to homozygosity for *CysGlyGln* of the β2-adrenergic receptor [Supplementary Table 2, http://links.lww.com/CM9/B913]. Therefore, *CysGlyGln* might serve as a biomarker for predicting the efficacy of β2-agonist therapy in AECOPD.

ICS, which are frequently used by patients with COPD, have variable outcomes and adverse reactions, which may be genetically influenced. Our review of the literature on the efficacy of inhaled glucocorticoids in COPD has identified several potential biological markers [Supplementary Table 2, http://links.lww.com/CM9/B913].

The mechanisms underlying the antioxidant effect of NAC on COPD are unknown. We reviewed studies investigating the effect of NAC treatment in patients with COPD with extremely slow/slow microsomal epoxide hydrolase (EPHX1) enzyme activity, and determined that NAC improved FEV1 and St. George's Respiratory Questionnaire (SGRQ) symptom scores, particularly in those with mild-to-moderate COPD [Supplementary Table 2, http://links.lww.com/CM9/B913]. In addition, *EPHX1* polymorphism may play an important role in differential responses to NAC treatment in patients with COPD.

ADRB2, *CHRM2*, and *CHRM3* were tested in 82 patients with COPD and 17 healthy smokers [Supplementary Table 2, http://links.lww.com/CM9/B913]. Among the polymorphisms investigated, the *CHRM2* polymorphism exhibited a significant association with poor responses to anti-cholinergic drugs.

In conclusion, this review summarizes the predictive ability of omics technology in COPD prognosis and treatment efficacy. Omics methods reveal the detailed pathogenesis of a disease, predicting future developments and curative effects, and suggesting new treatment approaches and technologies for future individualized treatment of COPD. Although omics approaches for predicting COPD prognosis and treatment efficacy remain at the basic research stage, follow-up studies may verify these relationships to identify crucial biomarkers for effectively predicting disease progression and treatment efficacy.

Conflicts of interests

None.

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