Abstract

Chronic obstructive pulmonary disease (COPD) is a chronic airway inflammation characterized by fixed airflow limitation and chronic respiratory symptoms, such as cough, sputum, and dyspnea. COPD is a progressive disease characterized by a decline in lung function. During the natural course of the disease, acute deterioration of symptoms leading to hospital visits can occur and influence further disease progression and subsequent exacerbation. Moreover, COPD is not only restricted to pulmonary manifestations but can present with other systemic diseases as comorbidities or systemic manifestations, including lung cancer, cardiovascular disease, pulmonary hypertension, sarcopenia, and metabolic abnormalities. These pulmonary and extrapulmonary conditions lead to the aggravation of dyspnea, physical inactivity, decreased exercise capacity, functional decline, reduced quality of life, and increased mortality. In addition, pneumonia, which is attributed to both COPD itself and an adverse effect of treatment (especially the use of inhaled and/or systemic steroids), can occur and lead to further deterioration in the prognosis of COPD. This review summarizes the long-term outcomes of patients with COPD. In addition, recent studies on the prediction of adverse outcomes are summarized in the last part of the review.

Keywords: Chronic Obstructive Pulmonary Disease; Outcome; Lung Function; Exacerbation; Mortality

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory airway disease characterized by persistent airflow limitation and related respiratory symptoms caused by airway and/or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases. However, COPD is not only a pulmonary disease but is also a systemic disease mediated by the activation of inflammatory pathways, hypoxemia-induced metabolic abnormalities, and physical inactivity-induced systemic consequences (Figure 1). Cigarette smoking and other noxious particles can induce a systemic inflammatory response and also directly enters the lungs and causes oxidative stress and tissue damage, leading to the development of COPD. Systemic and airway inflammation promote various systemic manifestations, and functional impairment of the lungs, decreased lung function-related hypoxemia, and physical inactivity can also lead to adverse outcomes.

COPD is a heterogeneous disease, and its prognosis is highly variable. Looking at the causes of COPD, smoking is one of the most obvious and well-known risk factors for COPD; however, biomass exposure and air pollution are also considered important risk factors for COPD. Moreover, approximately half of COPD development is attributed to abnormal lung growth caused by exposure to smoking during the perinatal period, respiratory infection, and a history of bronchial asthma in childhood. Therefore, a variable disease course and
prognosis are inevitable. When lung function declines, COPD-related respiratory symptoms and exacerbation events occur; as the disease progresses, systemic effects can also occur. Generally, exacerbation becomes more frequent and more severe as COPD progresses and in those with a previous exacerbation history. However, among 1,679 patients with COPD followed up for three years, 16% of exacerbation-naïve patients experienced new exacerbations, and even 5% experienced frequent exacerbations (≥2 events per year). In contrast, of the patients with frequent exacerbations, 5% had no subsequent exacerbations. This finding implies that the prognosis of COPD is highly variable among patients. This review article summarizes the long-term outcomes of COPD, focusing on pulmonary and systemic consequences. Subsequently, the risk of COPD-related and all-cause mortality is summarized, and recent studies of predictive tools for the prognosis of COPD are reviewed.

Pulmonary Outcomes

1. Exacerbation

Preventing exacerbation constitutes one of the two main goals of stable COPD treatment, along with reducing symptoms. In fact, exacerbation is not a frequent event during the course of COPD, but it is more likely to occur as COPD severity increases. In 2,138 patients enrolled in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study, exacerbation rates in the first year of follow-up were 0.85 events per person with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 2 disease, 1.34 for patients with stage 3 disease, and 2.00 for patients with stage 4 disease.

1) Exacerbation increases the risk of subsequent exacerbation

Exacerbation during the previous year was the single best predictor of subsequent exacerbations across all GOLD stages. One large cohort study that followed up patients for 17 years after the index COPD exacerbation event showed that as the frequency of exacerbation increased, further exacerbation risk increased.

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Figure 1. Chronic obstructive pulmonary disease (COPD) as systemic disease. RNS: reactive nitrogen species; ROS: reactive oxygen species; IL: interleukin; IFN: interferon; TNF: tumor necrosis factor; CRP: C-reactive protein; SAA: serum amyloid A. The figure was adapted from review article of Chan SM et al. Pathobiological mechanisms underlying metabolic syndrome (MetS) in chronic obstructive pulmonary disease (COPD): clinical significance and therapeutic strategies. Pharmacol Ther 2019;198:160-88, according to Creative Commons license.
The risk of subsequent severe exacerbation increased 3-fold after the second severe exacerbation and 24-fold after the 10th severe exacerbation compared to the first. Moreover, the median time to exacerbation for subsequent exacerbations was also shortened (approximately 5 years between the 1st and 2nd events and <4 months between the 9th and 10th).

2) Exacerbation leads to lung function decline
Exacerbation significantly influences the course of COPD. In the Genetic Epidemiology of COPD (COPDGene) study, changes in lung function over 5 years were analyzed. Forced expiratory volume in 1 second (FEV1) declined regardless of the severity of exacerbations. Annual FEV1 declined obviously in GOLD stage 1 and 2 groups. In particular, for a GOLD stage 1 subjects without exacerbation, FEV1 decline rate was ~25 mL/yr. However, the change in FEV1 for a GOLD stage 1 subjects with one, two, or three exacerbations of any severity can be estimated by excess decline per exacerbation event (~23 mL/yr), thus an annual rate of FEV1 change of ~48 mL/yr, ~71 mL/yr, and ~94 mL/yr, respectively. In GOLD stage 2, FEV1 declined ~19 mL/yr in subjects without exacerbation, but excess changes per exacerbation events of any severity was ~10 mL/yr. Although the decline rate was smaller than that of GOLD stage 1 or 2, in GOLD stage 3, the rate of FEV1 change was ~8 mL/yr, and there was an additional FEV1 decline of ~8 mL/yr per exacerbation event. Interestingly, there was no distinct change in lung function according to the presence or absence of an exacerbation history in GOLD 4 (~4 mL/yr in those without exacerbation and no excess change in subjects with exacerbation). This might be the result of survivor bias, which occurs as survival decreases as disease severity increases.

3) Association between exacerbation and lung cancer
Exacerbations prior to study enrollment were associated with future risk of lung cancer (odds ratio [OR], 1.39 per increased events [0, 1, and ≥2]; 95% confidence interval [CI], 1.04–1.85). In addition, lung cancer-associated mortality was compared between subjects with no acute exacerbations in the 12 months prior to enrollment (n=387) and those with one or more exacerbation in the same period (n=87). For the 8 years of follow-up, lung cancer-related mortality was higher in those with an exacerbation history (hazard ratio [HR], 2.752; 95% CI, 1.595–4.75).

4) The impact of exacerbation on survival
A cohort study that included 73,106 patients with COPD, who were hospitalized for exacerbation reported that mortality was 50% after 3.6 years and 75% after 7.7 years of follow-up. Meta-analysis of six relevant studies found exacerbation-related fatality occurred in 15.6% of cases. Moreover, severe exacerbation leads to higher mortality risks not only during hospitalization but also in the period after discharge and contributes substantially to total COPD mortality. The mortality rate increases as the frequency of exacerbations increases. Compared with individuals without an exacerbation history, the HR for mortality was 2.2 and 4.3 in those who had one or two exacerbations and three or more exacerbations, respectively.
ever smoker, (3) asthma with low smoking exposure and no airflow limitation, (4) COPD, (5) asthma-COPD overlap (ACO) with early onset asthma, and (6) ACO with late-onset asthma, after which the change in lung function was followed up for 18 years. Decline in FEV₁ was significantly faster in the COPD and ACO with late asthma onset groups (39.5 mL/yr and 49.6 mL/yr, respectively) compared with that in healthy never-smokers (20.9 mL/yr), ever-smokers (20.7 mL/yr), asthma (25.6 mL/yr), and ACO with early asthma onset groups (27.3 mL/yr).

2) The impact of FEV₁ decline
The risk of symptoms typical of COPD increases with declining lung function, especially with respect to percent predicted FEV₁. In addition, a decline in FEV₁ is associated with an increased risk of exacerbation. Among 2,138 patients with COPD in the ECLIPSE cohort, 31% had a total of 1,452 severe exacerbations, and the risk of severe exacerbation was increased 1.12 times with a 5% drop in percent predicted FEV₁. When only patients without prior exacerbation history were analyzed, the decrease in FEV₁ was still a significant risk factor for severe exacerbation (HR, 1.11; 95% CI, 1.07–1.15).

Furthermore, a decline in FEV₁ has been associated with survival. The survival rate of patients with COPD decreases as lung function decreases. The probability of survival in patients with COPD also decreases as FEV₁ decreases. The GOLD classification based on FEV₁ alone from GOLD stages 1 to 4 showed comparable predictive performance for discriminating mortality compared with the predictive performance of both exacerbation history and severity of dyspnea-based GOLD classification from GOLD stages A to D (area under the receiver operating characteristic curve, 0.62 vs. 0.65, respectively).

3) Pneumonia
1) Risk of pneumonia in COPD
The risk of community-acquired pneumonia (CAP) is higher in patients with COPD than in the general population, particularly in elderly patients with severe COPD. Of 40,414 patients with COPD, 3% experienced pneumonia, with an incidence rate of 22.4 per 1000 person-years. The odds ratios for pneumonia occurrence was 1.28 and 1.86 in patients aged ≥65 and ≥80 years. In addition, 19% of CAP patients had COPD, and 10% received a new diagnosis of COPD during hospitalization for CAP. These patients had a longer hospital stay and increased intensive care unit admission and mortality rates. Follow-up data for 22 years of hospital admission in the Copenhagen City Heart Study showed that patients with ACO with late asthma onset, COPD, and ACO with early asthma onset had a higher risk for acute hospital admission for pneumonia compared to never-smokers without disease (HR, 6.39, 3.67, and 3.56, respectively).

One meta-analysis of 11 studies involving 257,958 patients with COPD found that in hospitalized patients with pneumonia, COPD was not related to the duration of hospital stay, intensive care unit admission, or mortality. However, current guidelines recommend the use of inhaled corticosteroids (ICS) in combination with long-acting bronchodilators as an initial treatment only for COPD patients who exhibited clinical features of the Th2-cell signature, such as elevated blood eosinophil count in patients with GOLD group D disease who have more symptoms and a higher risk of exacerbation. Most of these patients have advanced COPD; thus, pneumonia is expected to have a significant influence on prognosis and should be considered.

2) Pathogenesis of pneumonia in COPD
There are shared risk factors between COPD and pneumonia, such as age and smoking. In addition, COPD itself increases susceptibility to pneumonia for reasons including impaired lung defense mechanisms (i.e., decreased mucociliary clearance); inflammation; shared inflammatory mediators in both COPD and pneumonia such as interleukin (IL)-1, IL-6, IL-8, matrix metalloproteinase (MMP)-8, and MMP-9; immune system alterations (i.e., activated CD8+ cytotoxic T cells); increased tracheobronchial microbial colonization; and rarely, α₁-antitrypsin deficiency. Furthermore, ICS also contribute to the development of pneumonia in COPD.

3) ICS and risk of pneumonia
The mechanism by which ICS influence the risk of pneumonia in COPD patients has not been clearly elucidated. ICS are thought to suppress the cellular and humoral arms of immunity, contributing to an increased risk of pneumonia in patients with COPD. ICS may alter the bactericidal effect of macrophages and reduce NO production. However, this relationship varies depending on the class and dose of ICS.

Meta-analysis of 55 studies involving 16,154 patients with COPD showed that an ICS dose greater than 1,000 μg of beclomethasone dipropionate equivalent per day (OR, 1.66; 95% CI, 1.38–2.00) was related to an increased risk of pneumonia. Another meta-analysis of 18 studies involving 49,828 patients with COPD analyzed the pneumonia risk according to the type of ICS and reported that fluticasone increased the risk...
of pneumonia more than budesonide or beclomethasone. In particular, fluticasone propionate has a higher risk of pneumonia than fluticasone furoate, and the effect of fluticasone, either propionate or furoate, on pneumonia is dose dependent.

4. Lung cancer

1) Association between lung cancer and COPD

Lung cancer and COPD are interrelated diseases that share risk factors, including cigarette smoking. Among patients with lung cancer, COPD was reported in 22%–52%, and COPD is regarded as major independent risk factor for lung cancer irrespective of smoking status. Figure 3 shows the overlap between COPD and lung cancer in smokers.

Meta-analysis reported the relative risk for lung cancer was 2.22 (95% CI, 1.66–2.97) in patients with COPD, 1.52 (95% CI, 1.25–1.84) in those with chronic bronchitis, and 2.04 (95% CI, 1.72–2.41) in those with emphysema. A Canadian public healthcare dataset, including 105,304 patients diagnosed with lung cancer, reported that spirometry was performed in 90.6% of patients with stage I or II lung cancer whereas in stage III or IV lung cancer, spirometry was performed in only 54.4%. Of the patients with lung cancer, 34.9% had been previously diagnosed with COPD. However, considering the low rate of spirometry in patients with advanced lung cancer, the actual prevalence of COPD in this patient population is expected to be higher. The National Lung Cancer Screening Trial (NLST), which included 13,939 current or former smokers aged 55–75 years, reported that the lung cancer rate per 1,000 person-years was 11.7 in COPD and 13.2 in ACO, which was much higher than that in smokers with asthma or with normal spirometry.

2) Pathogenetic link between COPD and lung cancer

Pathogenesis of lung cancer in COPD is not only associated with shared risk factors such as smoking exposure and aging, but also genetic susceptibility, epigenetic change, cell cycle regulation, chronic inflammation, oxidative stress, epithelial mesenchymal transition, and telomere shortening (Figure 4).

Lung cancer incidence is higher among patients with COPD, irrespective of smoking status, compared to those without COPD; the HR for lung cancer was 2.67 (95% CI, 2.09–3.40) in never-smokers with COPD and 6.19 (95% CI, 5.04–7.61) in ever-smokers with COPD relative to never-smokers without COPD during 7 years of follow-up in the National Health Insurance Service.
Cohort of 338,548 individuals aged 40–84 years. This result suggests that although smoking may further increase the risk of lung cancer, COPD itself contributes to the development of lung cancer.

3) Influence of COPD on course of lung cancer
COPD affects not only the development of lung cancer but also the treatment and survival of lung cancer patients. Overall survival is low in lung cancer patients with COPD (HR, 1.20; 95% CI, 1.19–1.22). Moreover, fewer surgical resections were performed and less adjuvant chemotherapy was administered to stage I or II lung cancer patients with COPD, and less palliative chemotherapy and radiation therapy were performed in stage III or IV lung cancer patients with COPD. Active treatment for lung cancer might be limited because of the reduced lung function and breathing difficulty in COPD, which in turn leads to a decrease in the survival of lung cancer patients with COPD. Even emphysema without COPD was associated with increased mortality in patients with lung cancer (HR, 2.3; 95% CI, 1.6–3.54). As the severity of visualized emphysema on chest computed tomography (CT) scans increases, survival is further reduced.

Extrapulmonary Outcomes

1. Clinical significance
The link between COPD and its systemic manifestations is thought to be multifactorial, including systemic inflammation, physical inactivity, and ventilation dysfunction (Figure 1). Risk factors for COPD, such as smoking exposure, genetic susceptibility, and treatment-related adverse effects, also contribute to the systemic consequences of COPD. Systemic manifestations, also called extrapulmonary complications or comorbidities, complicate the management of COPD and increase morbidity and mortality. Cardiovascular disease is the most common comorbid condition in COPD, however it did not significantly increase the mortality risk in COPD through a large national cohort study in Korea (adjusted HR, 1.14; 95% CI, 0.90–1.44 compared to non-COPD). Thus, herein, we focus on pulmonary hypertension and muscle dysfunction.

2. Pulmonary hypertension in COPD

1) Prevalence of pulmonary hypertension in COPD
Pulmonary hypertension (PH) can develop as the severity of COPD increases or can coexist idiopathically. The prevalence of PH reported varies depending on the diagnostic method or mean pulmonary arterial pressure (mPAP) cutoff value used for the definition of PH. Approximately 1%–5% of patients with COPD have an mPAP above 35–40 mm Hg, and approximately 90% of patients with GOLD stage IV COPD have an mPAP greater than 20 mm Hg.

2) Clinical importance of PH in COPD
In the COPDGene study, PH was defined as pulmonary artery to aortic diameter ratio greater than 1, and 819 of 6,109 patients (13.4%) were found to have PH. Additionally, PH was an independent risk factor for exacerbation; as PAP increased, the frequency of severe exacerbations increased. Another study of 362 patients with COPD who were referred for lung transplantation and underwent cardiac catheterization defined PH as mPAP >25 mm Hg and pulmonary artery occlusion pressure <16 mm Hg. Higher mPAP was associated with lower percent predicted FEV, and forced vital capacity, lower PO2 and higher PCO2 in the arterial blood. Furthermore, higher mPAP was also associated with right heart dysfunction and decreased exercise capacity (~11 m of 6-minute walking distance for every 5-mm Hg increase in mPAP). Among the 27 patients with chronic respiratory failure with PAP ≥40 mm Hg, COPD was present in 11 patients. Their median survival was 26 months, which was significantly shorter than that of patients with other causes of PH.

3) PH-targeting therapy in COPD with PH
Theoretically, smoking and emphysema promote endothelin-1 expression and reduce endothelial nitric oxide synthase expression in the pulmonary vasculature; thus, idiopathic pulmonary arterial hypertension (iPAH) targeted therapy was expected to be effective in COPD with PH. However, there were concerns about the aggravation of ventilation-perfusion mismatching by inhibiting hypoxic pulmonary vasoconstriction because of the pulmonary vasodilation effect. Herein, we summarize the results of previous studies on iPAH-targeting treatment of COPD with PH.

Table 1 summarizes the trials on COPD-PH; most included a small number of patients with conflicting results on clinical outcomes. One meta-analysis included nine trials of 365 patients: two trials used bosentan and seven trials used sildenafil. The results showed that PH-specific drugs reduced PAP and improved exercise capacity but did not affect dyspnea, quality of life, or hypoxemia. Recently, The Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) study compared the effects of PH medications in 375 patients with COPD with PH and 489 patients with iPAH. Although there was similar hemodynamic impairment at enrollment...
Table 1. Summary of PH targeted therapy in COPD with PH

| Citation       | Information of PH                                                                 | No. of patients and study design                                                                 | Drug for PH                      | Outcome statistics                                                                 |
|----------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|---------------------------------|-----------------------------------------------------------------------------------|
| Archer et al.  | Mean PAP >30 mm Hg or PVR >4 wood units, using intra-arterial catheter and Swan-Ganz catheter | Two center RCT involving 16 severe COPD patients with respiratory failure and PH                 | Prostacyclin vs. placebo        | Worsen (↓pO₂)                                                                     |
| Stolz et al.   | Echocardiography - PH at rest >30 mm Hg: 70% in bosentan, 60% in placebo group    | Single center RCT involving 30 patients of severe or very severe COPD                            | Bosentan vs. placebo, for 12 weeks | No significant improvement in 6MWD, lung function and PAP Worsen (↓pO₂, ↑A-a gradient, QOL) |
| Valerio et al. | mPAP >25 mm Hg, PCWP <15 mm Hg assessed by right heart catheterization            | RCT involving 32 COPD patients                                                                  | Bosentan vs. placebo, for 18 months | Improvement of PH and PVR, 6MWD, BODE index                                       |
| Wang et al.    | mPAP ≥25 mm Hg, assessed by right heart catheterization                           | Single center RCT involving 67 COPD patients                                                   | Iloprost inhalation             | Improved pulmonary hemodynamics without detrimental effects on PaO₂               |
| Vizza et al. (COMPERA) | 6th World Symposium on Pulmonary Hypertension recommendations (1) Moderate PH in COPD, defined as mPAP of 25 to 34 mm Hg or mPAP of 21 to 24 mm Hg with PVR of ≥3 Wood units; (2) and severe PH in COPD, defined as mPAP of >35 mm Hg or mPAP of ≥25 mm Hg with low cardiac index (<2.0 L/min/m²) | Cohort study for PH PH in COPD (n=375) - Moderate PH (n=68) vs. Severe PH (n=307) vs. IPAH (n=489) | PH in COPD vs. IPAH (%) - ERA monotherapy (3 vs. 11) - PDE-5i monotherapy (92 vs. 52) - Other monotherapy (1 vs. 9) - Other combination therapy (2.3 vs. 10) | Transplant-free survival rates were higher in the IPAH group than in the PH in COPD group at 1, 3, and 5 years - IPAH: 94%, 75%, and 55% vs. - COPD-PH: 86%, 55%, and 38% |
| Li et al.      | PAH using pulmonary ventilation imaging, pulmonary perfusion imaging, or echocardiography | Single center cohort study of COPD and PAH (n=90)                                                | Bosentan+sildenafil (n=50)       | Improvement of PAP and promote the recovery of cardiopulmonary function           |

*Includes soluble guanylate cyclase stimulators (COPD 0.05% vs. IPAH 2.7%) and calcium channel blockers (COPD 0.3% vs. IPAH 6.5%).

PH: pulmonary hypertension; COPD: chronic obstructive pulmonary disease; PAP: pulmonary arterial pressure; PVR: pulmonary vascular resistance; RCT: randomized controlled trial; pO₂: arterial oxygen pressure; 6MWD: six-minute walking distance; A-a gradient: alveolar–arterial gradient; QOL: quality of life; mPAP: mean pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; BODE: body mass index (B), degree of airflow obstruction (O), and dyspnea (D), and exercise capacity (E); IPAH: idiopathic pulmonary arterial hypertension; ERA: endothelin-receptor antagonist; PDE-5i: phosphodiesterase-5 inhibitor; PCA: prostacyclin analog; PAH: pulmonary arterial hypertension.
between groups, the COPD with PH group had worse transplantation-free survival than the iPAH group. However, 5-year survival in patients with COPD and PH who improved 6-minute walking distance by ≥30 m or by at least one World Health Organization functional class after 6±3 months of treatment was twice that of those who did not respond, particularly in patients with severe PH (mPAP ≥35 mm Hg or ≥25 mm Hg with cardiac index <2.0 L/min/m²). Another recent study showed better improvement in gas exchange and cardiac and pulmonary function following treatment bosentan with sildenafil (n=50) than with bosentan with iloprost (n=40) 43.

The effect of PH-targeting therapy on the prognosis of patients with COPD with PH remains inconclusive. Currently, the GOLD report recommends long-term oxygen therapy (LTOT) for those with an arterial PO₂ of 55–60 mm Hg or saturation of 88%, evidence of PH, congestive heart failure, or polycythemia. Until now, LTOT has been the most appropriate treatment for COPD with PH, although it has little effect on pulmonary hemodynamics and does not reverse pathological lesions of the pulmonary circulation. In addition, exercise rehabilitation and transplantation would be another choice of treatment for patients with COPD with PH 3.

3. Sarcopenia

1) Prevalence and mechanism of sarcopenia in COPD

Sarcopenia is the loss of skeletal muscle mass and strength that occurs with aging, but it is more prevalent in COPD compared to general population, with varying...
prevalence across studies ranging from 15% to 55%. The mechanism of sarcopenia in COPD is multifactorial, and the effects of smoking, hypoxemia, hypercapnia, inflammation triggering muscle proteolysis, muscle fiber switching, oxidative stress, mitochondrial dysfunction, and disuse atrophy are thought to be related (Figure 5).

2) Influence of sarcopenia on COPD
In COPD, muscle mass and exercise capacity are reduced, and peak heart rate and oxygen consumption during exercise are lower in single-leg knee extensor exercise. Moreover, muscle quality in COPD assessed using dual-energy X-ray absorptiometry and muscle biopsy have proven that fewer type 1 fibers and shift in fiber type distribution from type 1 to type 2 in the cross-sectional area of muscle are found in patients with advanced COPD.

Sarcopenia negatively affects the clinical course of COPD. Lower handgrip strength significantly correlates with more severe dyspnea, lower exercise tolerance, and higher exacerbation risk. Among 1,899 patients with COPD in the Copenhagen study, a lower fat-free mass index was observed in patients with more severe COPD and related to an increased risk of mortality.

Even smoking, regardless of COPD status, is regarded as an important risk factor for sarcopenia. Skeletal muscle weakness and decreased fatigue resistance can occur, even in asymptomatic smokers. It is presumed that the increase in cytokines and free radicals caused by cigarette smoke leads to muscle loss and myopathy.

3) Targeted therapy for sarcopenia in COPD
Several therapeutic attempts have been made to treat sarcopenia in COPD patients. Several trials on exercise with or without nutrition, anabolic steroids, ghrelin, and growth hormone showed positive effects on muscle mass, muscle strength, and exercise tolerance. In addition, oxygen therapy and a multidimensional approach of nutrition, exercise, and anabolic hormone had favorable effects on survival. Neuromuscular electrical stimulation comprises electrical stimulation of isolated muscles that evoke involuntary muscular contraction, improved muscle mass, strength, exercise tolerance, and dyspnea in several studies. Moreover, it is well-tolerated in patients with severe COPD and acute exacerbation. This passive form of exercise training may be helpful for those who cannot participate in an active pulmonary rehabilitation program.

Mortality of COPD
COPD is one of the leading causes of mortality worldwide and the third leading cause of death worldwide according to the World Health Organization in 2019. Respiratory issues were the most common cause of death in patients with COPD, followed by cardiac issues and cancer among 911 deaths in 6,184 patients. Approximately 40% of deaths were definitely or most likely related to COPD.

1. Factors related to COPD mortality
With more severe airflow limitation, all-cause mortality significantly increases relative to the normal spirometry group as a reference; HRs were 1.53, 2.09, 2.68, and 3.39 for GOLD stages I to IV, respectively (p for all <0.001). The Copenhagen study analyzed mortality over 22 years and showed that smoking and concomitant asthma history were related to the mortality. Compared to never-smokers without disease, both all-cause mortality and respiratory mortality were increased in ever-smokers without disease (HR, 1.46 and 1.90; p for both <0.001). Furthermore, COPD and ACO, with either early or late-onset asthma, had higher all-cause and respiratory mortality; the HR for all-cause mortality was 2.76, 2.55, and 3.72, respectively, and the HR for respiratory mortality was 10.45, 8.17, and 31.86, respectively. As the extent of emphysema increased on visual assessment of chest CT, mortality significantly increased.

2. Prediction of mortality and exacerbation risk
A lung health study of 5,887 patients followed up for more than 14 years, and 731 deaths were documented. Smoking cessation reduced cardiovascular-, lung cancer-, and respiratory-related causes of death relative to the usual care group. This suggests that intervention could contribute to better outcomes in COPD; if early identification of those who are at higher risk for exacerbation is possible, early interventions could be initiated. In this context, several attempts have been made to predict personalized prognosis in patients with COPD. Body mass index (B), degree of airflow obstruction (O), and dyspnea (D), and exercise capacity (E) measured using a 6-minute walk test are included in the BODE index, a multidimensional 10-point scale in which higher scores indicate a higher risk of death. The HR for death from any cause per one-point increase in the BODE score was 1.34 (95% CI, 1.26–1.42; p<0.001), and the HR for a respiratory cause of death was 1.62 (95% CI, 1.48–1.77; p<0.001). The ability of the BODE index to predict the risk of death was higher than that of FEV1 (C statistic
was 0.74 for the BODE index vs. 0.65 for FEV1). In addition, the BODE index showed better predictive ability for exacerbations in COPD than FEV1 alone. However, other clinical factors, such as comorbidities, COPD-related medications, and past exacerbation history, also contribute to COPD outcomes. Recently, studies have been conducted to better predict prognosis in various directions by reflecting these various clinical factors. The Acute COPD Exacerbation Prediction Tool (ACCEPT), which includes demographic (e.g., sex and age), clinical data (e.g., smoking status, FEV1, St. George's Respiratory Questionnaire, body mass index, and oxygen therapy), and medications including inhalers and cardiovascular disease-related statins, showed better performance for exacerbations, regardless of severity, compared to the predictive ability of “previous history of exacerbation” alone. Moll et al. used the COPD-Gene and Evaluation of COPD longitudinally to identify a predictive surrogate endpoint (ECLIPSE) cohort for demographics, spirometry, previous exacerbation history, comorbidities, extent of emphysema on chest CT, and exercise capacity to create a prediction model for mortality risk within 5 years using machine learning methods. This showed high predictive power compared to other existing COPD mortality prediction tools.

**Conclusion**

COPD is not restricted to the respiratory system only; because of its progressive nature with inflammation as a core pathology, it can affect pulmonary and extrapulmonary systems together. COPD is characterized by a progressive decline in lung function and related clinical symptoms and signs. Additionally, lung function decreases as the disease progresses, and exacerbation of respiratory symptoms can occur during the natural course of the disease. Treatment-related adverse effects, such as pneumonia, can also occur and negatively affect COPD prognosis. A decline in lung function, deterioriation of respiratory symptoms and exacerbation, exercise intolerance, inactivity, and decreased quality of life influence each other and eventually lead to adverse outcomes over time, resulting in an increased mortality risk. Predicting the adverse outcomes of COPD and initiating appropriate preventive strategies in advance are necessary, and a multidimensional approach is required.

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

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