



Chronic Obstructive Pulmonary Disease (COPD)--Failing To Prepare Means Preparing To Fail

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Abstract

The COVID-19 pandemic has accompanied rapid and sweeping changes in everyday life. According to a report by the World Health Organisation (WHO), the deaths due to lung diseases in India were on the rise accounting for 11 per cent of the total deaths. India has the dubious distinction of ranking first in lung disease deaths in the world. Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disease that causes obstructed airflow from the lungs. Chronic obstructive pulmonary disease (COPD) is the third leading cause of death globally only coronary heart disease and stroke claim more lives each year. But the COPD, which causes the small airways to taper and lung tissue to cease to work, has long been disregarded and neglected. COPD is common for ages 40 and older. COPD is a chronic disease that causes shortness of breath and makes breathing difficult and less effective. High prevalence places also have no cure. (Alpha 1) α 1-Antitrypsin deficiency is also related to the development of airflow obstruction. Its deficiency is a genetic cause of COPD and associated with more rapid decline in lung function. Over 2/3 of these deaths occurred in low- and middle-income countries (LMIC). COPD causes persistent and progressive respiratory symptoms, including difficulty in breathing, cough and/or phlegm production. The predominant thing to do is to stop cigarette, and cigar smoking. Treat the COPD patient with bronchodilators, which can help open the lungs. Emphysema and chronic bronchitis are the two most common conditions that contribute to COPD.

Keywords: Chronic obstructive pulmonary disease (COPD), Cystic fibrosis (CF), Airway epithelial cells (AEC), α 1-Antitrypsin, cytokines, lung cancer, pneumonia

Introduction

Cystic fibrosis (CF) is the most common genetic disease in the white population and results from mutations in a single gene encoding for a 1480

residue trans membrane glycoprotein, the cystic fibrosis trans membrane conductance regulator (CFTR). Lung disease, characterized by chronic neutrophilic inflammation, progressive airflow obstruction, and airway bacterial infections,

is the major cause of morbidity and mortality in patients with CF (1,2) Chronic obstructive pulmonary disease (COPD) is a major global health problem, and it is estimated to become the third leading cause of death worldwide by 2020; the disease is caused by both genetic and environmental factors; among these, cigarette smoking is the main risk factor for COPD and triggers an inflammatory response throughout the airways, in the alveoli, and in the pulmonary vasculature (3,4). Airway epithelial cells (AEC) are among the first sites of contact for inhaled insults and play a crucial role in maintaining normal airway function (5,6). Smoking is the most well-known risk factor for COPD; however, non-smokers may develop chronic airflow obstruction through occupational exposure to dust and chemicals and indoor pollution from biomass. (7) COPD is characterized by progressive airflow limitation from remodeling of small airways and destruction of lung parenchyma. (8)

COPD is associated with cardiovascular diseases, osteoporosis, diabetes, and metabolic syndrome more frequently than expected from common etiological factors. (9) The resulting tissue damage that occurs because of oxidative stress can help drive an inflammatory response (10). In chronic obstructive pulmonary disease (COPD), oxidative stress due to cigarette smoke is the main etiologic factor in disease pathogenesis (11). Lung cancer is the most frequently diagnosed cancer and the leading cause of cancer-related deaths worldwide, with approximately 10-20% 5-year survival rate. (12) Many studies showed that chronic obstructive pulmonary disease (COPD) is an important risk factor of lung cancer. (13) COPD is a common lung disease that includes chronic bronchitis and emphysema, exerts a high morbidity in the middle-aged and elderly population (14). Patients with acute exacerbation COPD (AECOPD) usually shows a sudden deterioration in lung function and ultimately death. (15, 16). Infections, tobacco, toxic particle inhalation and air pollution have all been reported to induce the excessive secretion of cytokines and chemotactic factors that can destroy the immune system. Studies have reported that inflammatory damage is the main causative factor of COPD progression. (17). Pneumonia is the lung

dis[ease] with the inflammation of terminal airway, alveoli, and pulmonary interstitial. Inflammation has been reported to enhance tumor development. (18,19) However, the mechanisms of inflammation-induced tumor development remain unclearly. Several studies also found that the levels of serum inflammatory cytokines in lung cancer patients can monitor the tumor development and prognosis. (20)

History;

The name chronic obstructive pulmonary disease is believed to have first been used in 1965. Previously it has been known by a number of different names, including chronic obstructive broncho-pulmonary disease, chronic airflow obstruction, chronic obstructive lung disease, nonspecific chronic pulmonary disease, diffuse obstructive pulmonary syndrome. The

terms emphysema and chronic bronchitis were formally defined as components of COPD in 1959 at the CIBA guest symposium and in 1962 at the American society Committee meeting on Diagnostic Standards. (21) Early descriptions of probable emphysema began in 1679 by T. Bonnet of a condition of "voluminous lungs". (22) In 1842, John Hutchinson invented the Spirometer, which allowed the measurement of vital capacity of the lungs. In 1953, Dr. George L. Waldbott, an American allergist, first described a new disease he named *smoker's respiratory syndrome* in the 1953 *Journal of the American Medical Association*. Modern treatments were developed during the second half of the 20th century. Evidence supporting the use of steroids in COPD was published in the late 1950s. (23) COPD develops slowly. Symptoms often worsen over time and limit the ability to do everyday activities.

Symptoms

- Chronic cough (often called "smokers' cough")
- SOB and difficulty in taking a deep breath
- Coughing up a lot of phlegm,
- Wheezing, Tightness of chest
- Frequent respiratory infections

Symptoms like chest tightness, wheezing, fatigue, breathing difficulties and respiratory infections then immediately consult your doctor.

Lung cancer cases in COPD patients can be reduced by steroids

Steroids can lower risk of lung cancer in COPD patients up to 30 pc. Pulmonary diseases are increasing more in women. Living in congested houses without good ventilation. Vulnerability to mosquito coil smoke at night. Frequent infection or stubborn allergic cough must be examined further.

India has become COPD capital of world

The severity of chronic obstructive pulmonary disease (COPD) in the country can be gauged by the fact that India has maximum cases of COPD in the world and ranks second when it comes to deaths caused by COPD, said Dr SN Gupta, consultant physician, pulmonary critical care and sleep medicine. India, with 35 million cases, has become the COPD capital of the world, while Uttar Pradesh shares 20% of India's burden. "Out of 15 lakh deaths due to COPD across the world, five lakh happen in India alone," he said addressing a press conference on Friday. He said COPD was causing more deaths than AIDS, TB, malaria and diabetes put together, but it remains highly neglected in the country. Delayed COPD diagnosis and poor COPD management was worsening the situation and leading patients to a condition referred to as 'lung attack'. "Diagnosis of lung attack is often based on the degree of worsening signs of COPD such as oxygen levels being lower than normal. Identifying the signs and symptoms of lung attack and getting timely help from physician is the best way to prevent further worsening of disease progression," said Gupta (24)

World COPD Day: Tips to manage a lung attack

Lung attacks or lung exacerbations are experienced by about a third of those suffering from chronic obstructive pulmonary disease (COPD). People diagnosed with this chronic disease often find themselves having a tough time to breath. COPD is a disease that obstructs air flows from the lungs, hampering one's ability to carry out daily chores with ease. A number of processes cause the airways to become narrow. There may be destruction of parts of the lung, mucus blocking the airways, and inflammation and swelling of the airway lining, as per WHO (World Health Organization) Dr S K

Jindal, Director, Jindal Clinics and former Professor & Head, Pulmonary Medicine, at Postgraduate Institute of Medical Education & Research tells us more about the disease, symptoms of a lung attack and stages of COPD on the occasion of World COPD Day (November 17).(25) COPD, if left untreated, can affect other organs: expert.

'Early stages of disease can be diagnosed by Spirometry'

Chronic Obstructive Pulmonary disease (COPD) is a chronic inflammatory lung disease that blocks up the lungs, leading to shortness of breath and difficulty in breathing. COPD gets worse over time, if untreated, and causes tremendous impact on the lives of patients and their families. The symptoms include shortness of breath and wheezing (whistling sounds during breathing), chronic or smoker's cough and chronic phlegm production. The World COPD Day is observed on November 20 to raise awareness among healthcare professionals and general public for prevention of chronic lung diseases. The theme for this year is: "All together to end COPD." "COPD is a disease of the small airways, which can take years for the symptoms to appear. The severity increases gradually and causes chronic obstruction. Unlike asthma, which is caused by allergens or hereditary factors, COPD is caused by smoking or other external factors like pollution," Dr. Madhusudhan Patrudu, Associate Professor, Government Hospital for Chest Diseases (GHCD), said. "Smokers should remember that apart from COPD, smoking can affect other organs like the heart and related disorders. COPD seems to be on the decline among both men and women. This is because smoking is on the decline and 'chulhas' (biomass fuel) by women, especially in rural areas, seems to be no longer in existence," he said. "The increased use of inhalers as a replacement for tablets, which was the only remedy in the past, is showing better results in the treatment of COPD. The drug reaches the lungs directly with getting deposited in other organs. Pulmonary Function Tests (PFTs) are being done at GHCD for detection of COPD," Dr. Patrudu said.(26)

All you need to know about the lung disease in India

According to World Health organization, Chronic Obstructive Pulmonary Diseases

e (COPD) may become the third leading cause of death worldwide by 2030. Likewise, according to a study published by the University of Washington's Global Burden Of Disease, COPD was the second-highest cause of death in India, after heart disease in the year 2017, killing 1 million (958,000). Thus, it is the need of the hour to tackle COPD at the right time. Dr Sameer Garde, Consultant Pulmonologist Global Hospital Mumbai, talks about this fatal lung disease and also its prevention. Do you find it difficult to breathe freely? Are you unable to concentrate on your work owing to that constant cough? Did you miss your important meeting owing to that chest tightness and wheezing? Then, it is time you should visit your doctor as it could be Chronic Obstructive Pulmonary Disease (COPD).(27)

COPD--"And the fire fury on"

Smoking: It is a higher risk of COPD. Even second-hand smoking is equally harmful and can be equally charged with crime.

Dust and chemicals: Respiratory apparatus may get puffed owing to continuous exposure to the harmful chemicals and also the dust along with irritating the lungs.

Pollution: The harmful chemicals emitted by the vehicles or chemical industries and fumes from that burning fuel for cooking can also lead to COPD. Keep away from using mosquito repellents in the form of Coils/liquids/ mats; also stop burning Incense sticks/camphor etc. the pollution created by these items is as substandard as smoking!

India's COPD death rate among world's highest

India has among the world's highest death rates from chronic obstructive pulmonary disease (COPD), according to new research that some health experts say reinforces concerns about gaps in diagnosis flagged earlier. COPD is an inflammatory lung disease that causes obstructed airflow from the lungs. The symptoms include breathing difficulties, cough, mucus (sputum) production and wheezing. A worldwide study has estimated that India's death rate from COPD during 2019 was 98 per 100,000 population, three times the American rate of 33 and the British rate of 31 although the three countries had comparable prevalence rates 3,300 to 3,700 per 100,000 population. The study, based on latest data

from 204 countries or regions and published in the *British Medical Journal*, has also found that while COPD rates have declined in many countries over the past three decades, absolute counts have increased with smoking and air pollution contributing to the disease burden.

India has become COPD capital of world

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of the hour to tackle COPD at the right time. Dr Sameer Garde, Consultant Pulmonologist, Global Hospital Mumbai, talks about this fatal lung disease and also its prevention. Do you find it difficult to breathe freely? Are you unable to concentrate on your work owing to that constant cough? Did you miss your important meeting owing to that chest tightness and wheezing? Then, it is time you should visit your doctor as it could be Chronic Obstructive Pulmonary Disease (COPD).(27) Infections, tobacco, toxic particle inhalation and air pollution have all been reported to induce the excessive secretion of cytokines and chemo tactic factors that can destroy immune system (28).

Small-Airway Disease; Inflammation and peribronchial fibrosis contribute to the fixed airway obstruction in the small airways in COPD, and progression of the inflammation, resulting in destruction of the alveolar attachments on the outer walls of the small airways, may also contribute.

Inflammation; Studies of lung or bronchial biopsies and induced sputum have shown evidence of lung inflammation in all cigarette smokers. However, it appears that an enhanced or abnormal inflammatory response to inhaled particles or gases, beyond the normal protective inflammatory response in the lungs, is a characteristic feature of COPD and has the potential to produce lung injury. In the bronchial mucosa in patients with COPD, T lymphocytes predominate, mainly CD8⁺ cells and macrophages. It has been suggested that the presence of increased CD8⁺ T lymphocytes differentiates between smokers who do and do not develop COPD and that there is a correlation between T-cell numbers, the amount of alveolar destruction, and the severity of airflow limitation. However, smokers with normal lung function also show, to a lesser extent, an increased number of CD8⁺ cells compared with control non-smokers. Circulating CD8⁺ cells are also increased in number in patients with COPD who do not smoke, and there is an increase in CD4⁺ cells in patients with COPD, particularly as the disease progresses. This suggests chronic immune stimulation. It may be that chronic colonization of the lower respiratory tract of patients with COPD by bacterial and viral pathogens is responsible for this enhanced inflammatory response. It is also possible that cigarette smoke itself damages airway cells, creating new auto antigens that drive the immune inflammatory response. (29)

Proteases and anti-proteases; Elastin is an important target for proteolytic enzymes, and its destruction results in loss of elasticity in the lung parenchyma. Elastin are the principal component of elastic fibers and are secreted from several cell types as a precursor, tropoelastin. These tropoelastin molecules become aligned in the extracellular space on microfibrils. Because the cross-links, known as desmosines, are unique to elastin, they have been used as a marker of elastin degradation.(30) Desmosine and elastin peptides are elevated in smokers and patients with COPD.

Role of oxidants and antioxidants in smoking-induced COPD; Cigarette smoke is a complex mixture of more than 4,700 chemical compounds, including high concentrations of free radicals and other oxidants. Other sources of reactive oxygen species are those generated through normal cellular processes in the lungs, such as those produced by normal cellular respiration or by inhalation of air pollutants such as particulate pollution. A delicate

balance exists between the toxicity of oxidants and the protective effects of intra- and extracellular antioxidant defense systems, which are critically important for the maintenance of normal pulmonary cellular functions. A shift of the oxidant/antioxidant balance in favor of oxidants is known as oxidative stress. There is now considerable evidence of increased oxidative stress in smokers and in patients with COPD (31).

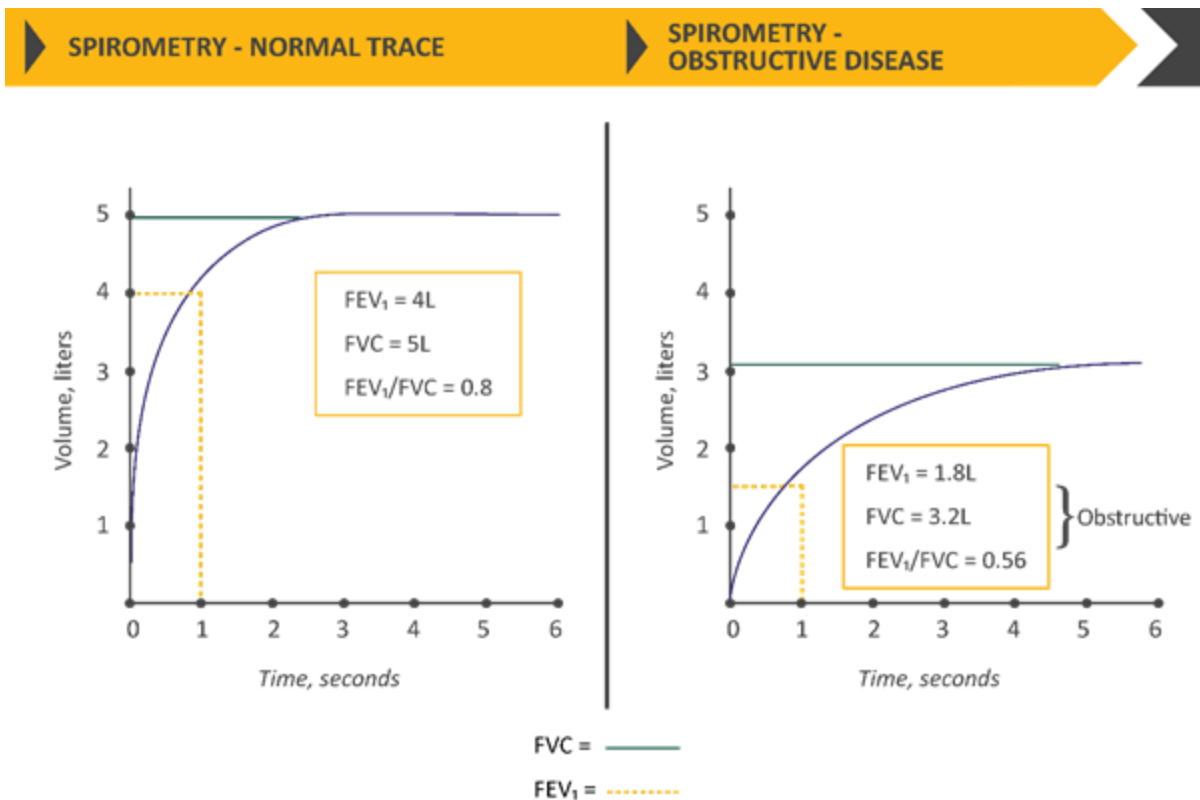
Laboratory diagnosis of COPD; COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease. Spirometry is required to make the diagnosis; the presence of a post-bronchodilator FEV1/FVC < 0.70 confirms the presence of persistent airflow limitation. The goals of COPD assessment are to determine the level of airflow limitation, the impact of disease on the patient's health status, and the risk of future events (such as exacerbations, hospital admissions, or death), in order to guide therapy.

▶ KEY INDICATORS FOR CONSIDERING A DIAGNOSIS OF COPD

Consider COPD, and perform spirometry, if any of these indicators are present in an individual over age 40. These indicators are not diagnostic themselves, but the presence of multiple key indicators increases the probability of a diagnosis of COPD. Spirometry is required to establish a diagnosis of COPD.

Dyspnea that is:	Progressive over time. Characteristically worse with exercise. Persistent.
Chronic Cough:	May be intermittent and may be unproductive. Recurrent wheeze.
Chronic Sputum Production:	Any pattern of chronic sputum production may indicate COPD.
Recurrent Lower Respiratory Tract Infections	
History of Risk Factors:	Host factors (such as genetic factors, congenital/developmental abnormalities etc.). Tobacco smoke (including popular local preparations). Smoke from home cooking and heating fuels. Occupational dusts, vapors, fumes, gases and other chemicals.
Family History of COPD and/or Childhood Factors:	For example low birthweight, childhood respiratory infections etc.

Spirometry; Suspected COPD should be confirmed using spirometry. The National Heart, Lung, and Blood Institute recommends spirometry for all smokers 45 years or older, particularly those who present with shortness of breath, coughing, wheezing, or persistent sputum production. Although spirometry is a simple procedure that can be performed in the out-patient room, it is underused by primary care physicians.



The key spirometric features of COPD are FEV1 and forced vital capacity (FVC). FEV1 is the volume of air that a patient can expire in one second following a full inspiration. The FVC is the total maximum volume of air that a patient can exhale after a full inspiration. A postbronchodilator FEV1/FVC ratio of less than 0.7 associated with an FEV1 of less than 80 percent of the predicted value is diagnostic of airflow limitation and confirms COPD. A patient's FEV1 relative to the predicted values in persons of similar age, sex, and height further characterizes the degree of airflow obstruction.(32).

CLASSIFICATION OF AIRFLOW LIMITATION SEVERITY IN COPD (BASED ON POST-BRONCHODILATOR FEV₁)

In patients with FEV₁/FVC < 0.70:

GOLD 1:	Mild	FEV ₁ ≥ 80% predicted
GOLD 2:	Moderate	50% ≤ FEV ₁ < 80% predicted
GOLD 3:	Severe	30% ≤ FEV ₁ < 50% predicted
GOLD 4:	Very Severe	FEV ₁ < 30% predicted

The American Thoracic Society, European Respiratory Society, Global Initiative for Chronic Obstructive Lung Disease, and British Thoracic Society have published guidelines for classifying COPD severity based on spirometry findings. Disease severity is essential in determining the appropriate

therapy for each patient. Spirometry can also be used to track disease progression over time. Peak expiratory flow rates are not helpful in diagnosing COPD because they can underestimate the level of airway obstruction.

Other Diagnostic Tests

Spirometry is the key test for diagnosing COPD; however, several additional tests are useful to rule out concomitant disease. Chest radiography should be performed to look for evidence of lung nodules, masses, or fibrotic change. Repeated or annual chest radiography and computed tomography to screen for lung cancer or to monitor the disease are not recommended. A complete blood count should be performed to exclude anemia or polycythemia. It is reasonable to perform electrocardiography and echocardiography in patients with signs of cor pulmonale to evaluate pulmonary circulatory pressures. Pulse oximetry at rest, with exertion, and during sleep should be performed to evaluate for hypoxemia and the need for supplemental oxygen.

Conclusion

Lung transplantation was the only option to treat pulmonary fibrosis, COPD, cystic fibrosis and other end-stage respiratory diseases. Unfortunately awareness on the benefits of lung transplantation was poor even in the medical community with several patients being deprived of its benefits. Respiratory diseases were no longer restricted to the elderly but were now being detected even in younger age groups. Lung transplantation which was much cheaper in the country when compared to most developed countries could improve the quality of life and expand lifespan for end-stage lung disease patients, Dr Balasubramani said, in a meeting (33)

References

1. Ratjen F., Döring G. Cystic fibrosis. *The Lancet*. 2003;**361**(9358):681–689.
2. Elborn J. S. Cystic fibrosis. *The Lancet*. 2016;**388**(10059):2519–2531.
3. Decramer M., Janssens W., Miravittles M. Chronic obstructive pulmonary disease. *The Lancet*. 2012;**379**(9823):1341–1351.
4. Barnes P. J., Burney P. G. J., Silverman E. K., et al. Chronic obstructive pulmonary disease. *Nature Reviews Disease Primers*. 2015;**1**, article 15076
5. Gao W., Li L., Wang Y., et al. Bronchial epithelial cells: the key effector cells in the pathogenesis of chronic obstructive pulmonary disease? *Respirology*. 2015;**20**(5):722–729.
6. Tam A., Wadsworth S., Dorscheid D., Man S. F. P., Sin D. D. The airway epithelium: more than just a structural barrier. *Therapeutic Advances in Respiratory Disease*. 2011;**5**(4):255–273
7. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Lung Disease 2017 Report; 2017. GOLD Executive Summary.
8. Barnes PJ. Chronic obstructive pulmonary disease: Effects beyond the lungs. *PLoS Medicine*. 2010;**7** 3:e1000220.
9. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *The European Respiratory Journal*. 2008;**32**(4):962–969
10. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Ahme-din J. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015; **65**(2):87-108.
11. Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet*. 2018;**391**(10125):1023-1075.
12. Sanchez-Salcedo P, Berto J, De-Torres JP, et al. Lung cancer screening: fourteen year experience of the Pamplona Early Detection Program (P-IELCAP). *Arch Bronconeumol*. 2015;**51**(4):169-176.
13. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. Gold executive summary. *Am J Respir Crit Care Med*. 2017;**195**(5):557-582.—
14. Chen H, Wang Y, Bai C, Wang X. Alterations of plasma inflammatory biomarkers in the healthy and chronic obstructive pulmonary disease patients with or without acute

- exacerbation. *J Proteomics*. 2012;75(10):2835-2843.
15. Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. *J Allergy Clin Immunol*. 2016; 138(1):16-27.
 16. Elinav E, Nowarski R, Thaiss CA, et al. Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. *Nat Rev Cancer*. 2013; 13(11):759-771.
 17. Brenner DR, Fanidi A, Grankvist K, et al. Inflammatory cytokines and lung cancer risk in 3 prospective studies. *Am J Epidemiol*. 2017; 185(2):86-95.
 18. Marrugal A, Ojeda L, Paz-Ares L, Molina-Pinelo S, Ferrer I. Proteomic-based approaches for the study of cytokines in lung cancer. *Dis Markers*. 2016; 2016:2138627.
 19. Hsieh HL, Tsai MM. Tumor progression-dependent angiogenesis in gastric cancer and its potential application. *World J Gastrointest Oncol*. 2019; 11(9):686-704.
 20. Kim MY, Oskarsson T, Acharyya S, et al. Tumor self-seeding by circulating cancer cells. *Cell*. 2009;139(7):1315-1326.
 21. Rose-John S. IL-6 trans-signaling via the soluble IL-6 receptor: importance for the pro-inflammatory activities of IL-6. *Int J Biol Sci*. 2012;8(9):1237-1247
 21. Petty TL (2006). "The history of COPD". *International Journal of Chronic Obstructive Pulmonary Disease*. 1 (1): 3–14.
 22. Wright JL, Churg A (2008). "Pathologic Features of Chronic Obstructive Pulmonary Disease: Diagnostic Criteria and Differential Diagnosis(PDF)". In Fishman A, Elias J, Fishman J, Grippi M, Senior R, Pack A (eds.). *Fishman's Pulmonary Diseases and Disorders* (4th ed.). McGraw-Hill. pp. 693–70
 23. Fishman AP (May 2005). "One hundred years of chronic obstructive pulmonary disease". *American Journal of Respiratory and Critical Care Medicine*. 171 (9): 941–8.
 24. Hindustan times--Published on Nov 08, 2019 09:53 PM IST Published on Nov 16, 2021 07:01 PM IST--Hindusthan times_
 25. SPECIAL CORRESPONDENT, Visakhapatnam, November 20, VISAKHAPATNAM NOVEMBER 20, 2019, Deccan chronicle, November, 26, 2019
 26. Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. *J Allergy Clin Immunol*. 2016; 138(1):16-27
 27. Celli BR, MacNee W; ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;23:932–946
 28. Harel S, Janoff A, Yu SY, Hurewitz A, Bergofsky EH. Desmosine radioimmunoassay for measuring elastin degradation *in vitro*. *Am Rev Respir Dis* 1980;122:769–773.
 29. MacNee W. Oxidative stress and lung inflammation in airways disease. *Eur J Pharmacol* 2001;429:195–207
 30. Global initiative for COPD, Pocket guide to management and prevention-2022-Report.