Review Article

Emerging Molecular and Clinical Challenges in Managing Lung Cancer Treatment During the COVID-19 Infection

ABSTRACT

The COVID-19 pandemic now had a broad impact on the health care system since its start. Cancer patients, specifically lung cancer patients, are undergoing a more vulnerable group due to their complex pathophysiological and immunological characteristics. Therefore, they need more attention and care about health and treatment. It is yet unknown how SARS-CoV-2 (COVID-19) infected lung cancer patient's health and management of treatment impacts them. From a clinical and multidisciplinary perspective, we aimed to explain our main priorities concerning COVID-19 infection in the scenario of lung cancer patients' group in this chapter. Various types of lung cancer therapeutic strategies, including chemotherapy, radiation therapy, and immunotherapy, can all significantly increase the risk, therefore making a patient's chances of a poor outcome higher. Patients with lung cancer need regular clinical and radiologic examinations and follow-ups, which the COVID-19 pandemic might hamper. COVID-19-related lung cancer patients' incidental radiologic abnormalities might show up in regular radiology exams, making it challenging to understand disease progression and the effect of therapy.The COVID-19 pandemic has profoundly impacted lung cancer care, highlighting challenges in patient management, treatment outcomes, and ethical dilemmas. Quantitative analysis and exploration of future directions would enhance clinical and research impact. In addition, cancer treatment-induced pneumonitis can exhibit radiologic characteristics that are identical to those seen in acute SARS-CoV-2 pneumonia, possibly due to a wrong diagnosis and misinterpretation. The current COVID-19 health crisis is affecting many healthcare requirements, including the necessity for regular healthcare accessibility, particularly follow-ups, and the clinical trials in which this patient group may be included. The COVID-19 epidemic has placed healthcare practitioners, scientists, researchers, and institutions in a complex and dangerous situation, forcing them to address challenges with ethical scenarios.

Keywords: *COVID-19, Lung cancer, Signaling molecular, Epigenetic regulation, COVID-19 pandemic*

1. INTRODUCTION

The severe acute respiratory syndrome (SARS) coronavirus (COV), commonly known as SARS-CoV-2, causes Coronavirus Disease 2019 (COVID-19), which is a respiratory tract infection. COVID-19 was originally identified in Central China (Wuhan, the capital of Hubei province) towards the end of December 2019, and has quickly spread to other nations throughout the world **[1]**. The majority of SARS-CoV-2 infected patients were asymptomatic or had moderate upper respiratory tract symptoms, according to statistics from China and Italy, the first two nations with the highest incidence. Unfortunately, around 14% to 24% of patients had pneumonitis, necessitating hospitalization for oxygen support. Acute respiratory distress syndrome (ARDS) and sepsis-related acute organ failure occurred in around 5% of patients, necessitating hospitalization into the intensive care unit (ICU). The number of reported case fatality rates (CFR 14%) is much greater in COVID-19-positive individuals with underlying concurrent illnesses, such as cancer, diabetes, cardiovascular disease, and chronic pulmonary disease, and many who are older.

Various methodologies of SARS-CoV-2 diagnosis could help explain why the incidence and CFR are so different. In the beginning, Italy used a non-discriminatory testing methodology encompassing symptomatic and asymptomatic COVID-19 patients. However, within a week of 6 days, when a large number of patients developed severe SARS-CoV-2-related ARDS, the Italian Ministry of Health decided to only permit testing in symptomatic patients who were potential hospitalization candidates, which may have resulted in a biased selection and delayed treatment of these COVID-19 patients. In this chapter, we want to emphasize the importance of early diagnosis and treatment of lung cancer patients within a specific population for COVID-19 testing prioritizing **[2]**. Smoking history has been linked to a greater incidence and severity of SARS-CoV-2 infection depending on existing data **[3, 4]**. The risk of severe symptoms is 1.4 substantially larger (RR 1.4, 95% CI: 0.98-2.00), and the risk of mechanical ventilation, intensive care unit (ICU) admission, or mortality of patients is 2.4 substantially larger (RR 2.4, 95 % CI: 1.43-4.04) in smokers compared to non-smokers **[5]**. The two major tobacco-related impairments that contribute to susceptibility to COVID-19 infections also induce structural and immunologic modifications **[6]**. Moreover, the changes in the macrophage, humoral, and cell-mediated immune responses can also enhance the immunosuppressive effects **[7, 8]**. Prior tobacco-related lung damage, such as chronic obstructive pulmonary disease (COPD) and lung cancer, may also lead to more serious difficulties arising during COVID-19 infection **[4]**.

In the high COVID-19 prevalence, morbidity and mortality appear to be linked to all types of cancers. Lung cancer introduces a unique set of risk factors for COVID-19 health problems, such as substantial cardiovascular and respiratory co-morbidities due to aging, smoking-related lung damage, and the essential introduction of immunological drugs for immune suppression or impairment **[9, 10]**. COVID-19 infection can also enhance pulmonary architectural defects caused by mechanical tumor obstruction or previous lung surgery.

2. EPIDEMIOLOGICAL CHARACTERISTICS OF CANCER PATIENTS ASSOCIATED WITH COVID-19 INFECTION

On a daily basis, humans are exposed to a variety of infections, and based on infection, human immune systems are responded to by the involvement of immune cells and other molecules in the vascular system. Inflammation is defined as the process of removing the

'trigger,' reducing damage, eliminating damaged cells/tissues, and then activating repair mechanisms **[11]**. Acute inflammation is quick and short-lived, but chronic inflammation is slower and lasts longer, and these two different subtypes of inflammation differ significantly in the mechanism by which various types of cells are mobilized, with acute inflammation involving granulocytes and chronic inflammation involving agranulocytes **[12]**. Lung damage caused by acute inflammation can result in acute respiratory distress syndrome (ARDS). Cancer, heart disease, diabetes, asthma, chronic obstructive pulmonary disease (COPD), arthritis, and Alzheimer's are chronic disorders that may be caused by chronic inflammation. As a result, inflammation is a key indicator that damages cells and organ systems, and it has a serious rolein the pathogenesis of both acute and chronic diseases. Prolonged inflammation can activate secondary infection and enhance vulnerabilities to microorganism-caused injuries and infections, including bacteria and viruses like SARS-CoV-2. Several respiratory diseases and lung cancer are chronic diseases connected to the same type of inflammation.

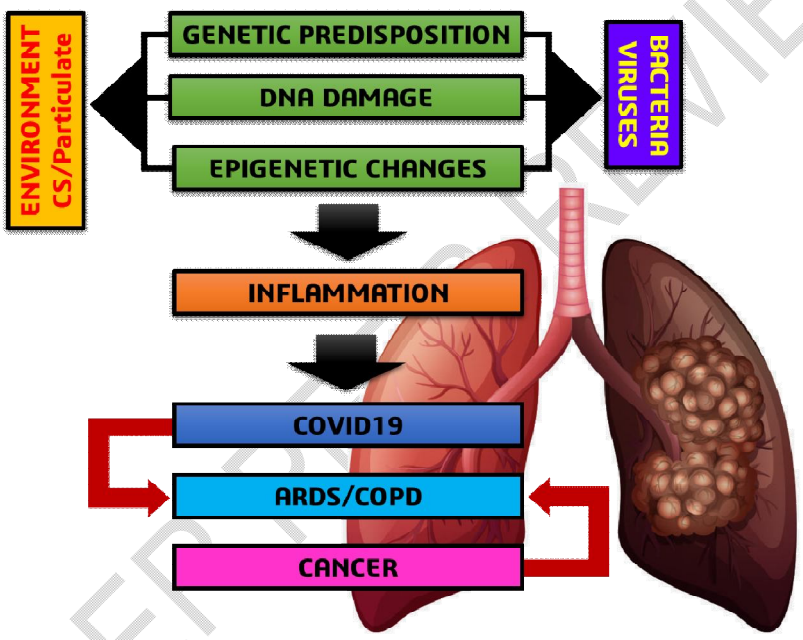

Figure 1. Inflammation connects COVID-19 and cancer with pulmonary diseases. In addition to genetic predisposition, several extrinsic factors, such as bacterial/viral infections and environmental agents, can cause inflammation, with an emerging realization of the involvement of epigenetic regulation. Inflammation leads to pulmonary manifestations exemplified by ARDS and COPD, which are observed in COVID-19 and lung cancer patients.

Chronic inflammatory responses are very well recognized and cause diseases including asthma, COPD, and pulmonary fibrosis **[13]**. Similarly, the function of inflammation responses in cancer is widely recognized **[14, 15]**. Inflammation enhances tumor growth, and cancer-related inflammation influences numerous essential characteristics of cancer, including tumor cell proliferation and survival, angiogenesis, metastasis, and therapeutic intervention **[16]**. The classical research is focused on the study of genetic and molecular markers of inflammation, but nowadays modern research is more focused on epigenetic effects of genetic and environmental factors of inflammation **[17-21]**. In the case of unidentified molecular mechanisms and their targets of various chronic inflammatory

diseases are targeting epigenetic modifications (gene expression alterations that are hereditary and unrelated to alterations in DNA sequence) might be a potential treatment option **[22, 23]**. The inflammation tends to be associated with various lung diseases, cancer, and COVID-19 **(Figure. 1)**, so there is an increasing interest in finding more about the epigenetic basis of inflammation. This section aims to provide a thorough understanding of the fundamental mechanisms.

3. CHALLENGES IN LUNG CANCER THERAPY DURING THE COVID-19 PANDEMIC

Nowadays, coronavirus disease 2019 (COVID-19) has been continuously mutated and identified as a new type of coronavirus family strain known as acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has evolved rapidly into a worldwide pandemic responsible for public health emergency and primary international concern**[24, 25]**. As a result, there is a massive rearrangement of healthcare settings such as hospitals and diagnostic centers, and professionals are required in both places throughout the world to address this medical emergency with a massive number of COVID-19-positive individuals receiving hospitalization and intensive care facilities**[26]**. Patients with associated chronic conditions, such as lung cancer, are highly concerned about another broad reallocation of health resources. Physicians are rapidly becoming a directed mode of specific treatment select for specific patients will undergo chemotherapeutic treatment based on who is the more expected to get a positive result due to the primacy of health support for COVID-19 patients, that is causing concern in the medical oncology community **[27]**. Due to the obvious and considerable possibility of COVID-19 interrupting patients' appropriate diagnosis and therapy management for treating medical professionals, this already unclear picture appears to be considerably more terrible for patients with lung cancer.

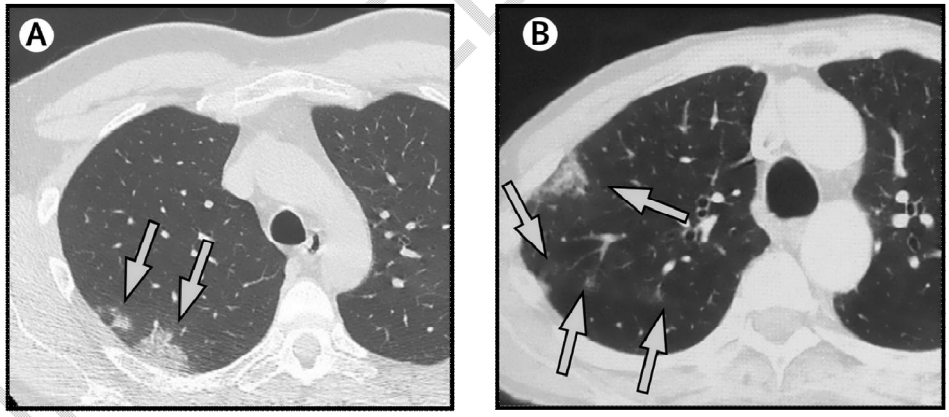

Figure 2. CT scans of pneumonia due to COVID-19 and immune checkpoint inhibitor therapy **(A)** Axial lung image (without intravenous contrast) of a 49-year-old man with COVID-19, showing two sub-solid areas in the upper right lobe (arrows). **(B)** Axial lung image (without intravenous contrast) of an immune checkpoint inhibitor-treated 76-year-old man with metastatic melanoma, showing a sub-solid area and ground-glass opacities with a rounded morphology in the upper right lobe (arrows). COVID-19=coronavirus disease 2019.

COVID-19 clinical diagnoses range from asymptomatic to moderate symptoms (such as a cold, fever, cough, or other non-specific indications) to serious pneumonia resulting in acute respiratory distress syndrome, which affects 17–29% of infected people. A COVID-19-related death has been documented in roughly 3% of COVID-19-positive individuals in the

Chinese population, whereas more excellent mortality rates have been observed in Italy, which contains the second largest number of verified COVID-19 cases globally after the United States **[28-30]**.The multifocal peripheral and basal ground-glass opacities, crazy paving patterns, traction bronchiectasis, and air bronchogram-like clinical signals are among the most common CT findings in the early phases of COVID-19-induced pneumonia.These radiological findings can be confused with CT abnormalities that are frequently seen in patients with lung cancer as their illness progresses or if concurrent pneumonia develops as a result of an overlapping active pathogen. Fromthe perspective of clinical characteristics, the worsening of pulmonary symptoms as lung cancer progresses might be identical to that observed in COVID-19, which is challenging for comprehensive evaluation of the disease's prognosis in lung cancer patients **(Figure. 2) [31, 32]**.

These similarities can make it difficult for doctors to figure out the difference between lung cancer progression and a predicted COVID-19 super-infection based on radiological and clinical evidence, but, more critically, these illnesses require completely distinct treatment methods. Pneumonitis can also be caused by immune checkpoint inhibitor therapy, which is an effective and extensively used requirement of treatment for lung cancer across a range of therapeutic approaches and circumstances **[33]**. The pneumonitis caused by immune checkpoint inhibitors has been observed in roughly 2% of cancer patients, with a greater frequency in lung cancer patients **[34, 35]**. Particularly in comparison to COVID-19 infection, immune checkpoint inhibitor-induced pneumonitis has a wide range of clinical symptoms, including cough (or exacerbation of cough), chest discomfort, dyspnea, and fever. Furthermore, CT examination of immune checkpoint inhibitor-related pneumonitis reveals radiological features that are comparable to COVID-19-induced pneumonia **(Figure 2)**, making differentiation between both clinical categories challenging. Alternatively, tyrosine kinase inhibitors can cause interstitial-like pneumonitis observed in radiological patterns, which occurs in 4% of treated patients with osimertinib who are already diagnosed with epidermal growth factor receptor-mutant lung cancer **[36]**.

The standard chemotherapy doesn't show up to become a suitable or potentially safer alternative to immune checkpoint inhibitor therapy in this circumstance, neither treating doctors who would like to avoid overlapping immune checkpoint inhibitor- and COVID-19-related radiological and clinical changes nor for patients who are inappropriate for this immunotherapy. First, in a large population of patients lacking oncogene-driven lung cancer and significantly high PD-L1 expression in tumor cells, combinations of chemotherapies and immunotherapies have demonstrated the highest effectiveness and have become the standard of treatment. Second, chemotherapy-associated pneumonitis has been reported in up to 16% of treated individuals, and cytotoxic chemotherapy has immunosuppressive properties. Chemotherapy given within a month of a COVID-19 diagnosis has been linked to a greater risk of infection-related severe consequences **[9, 37-39]**. Anticancer therapy cannot be delayed or postponed due to the clinical and biological aggressiveness of lung cancers. As a result, specific evidence-based guidelines are required. The complete therapy of patients with lung cancer during the COVID-19 pandemic should include greater attention to both clinical and radiological pulmonary symptoms than patients with other different types of cancers.

4. IMPACT OF COVID-19 ON LUNG CANCER PROGNOSIS

The Kaplan–Meier survival analysis revealed that lung cancer patients with a prior history of COVID-19 exhibited reduced progression-free survival (PFS) and progression-free survival in combination (PFSC); however, these differences did not reach statistical significance (Figure 3). Cox proportional hazards regression analysis indicated that lung cancer patients

with a history of COVID-19 had shorter PFS (Model II: HR = 3.28, 95% CI: 1.6–6.72; Model III: HR = 3.39, 95% CI: 1.45–7.95) and PFSC (Model II: HR = 2.83, 95% CI: 1.39–5.76; Model III: HR = 3.84, 95% CI: 1.67–8.84) compared to those without COVID-19, after adjusting for potential confounding variables (Table 1)**[141]**.

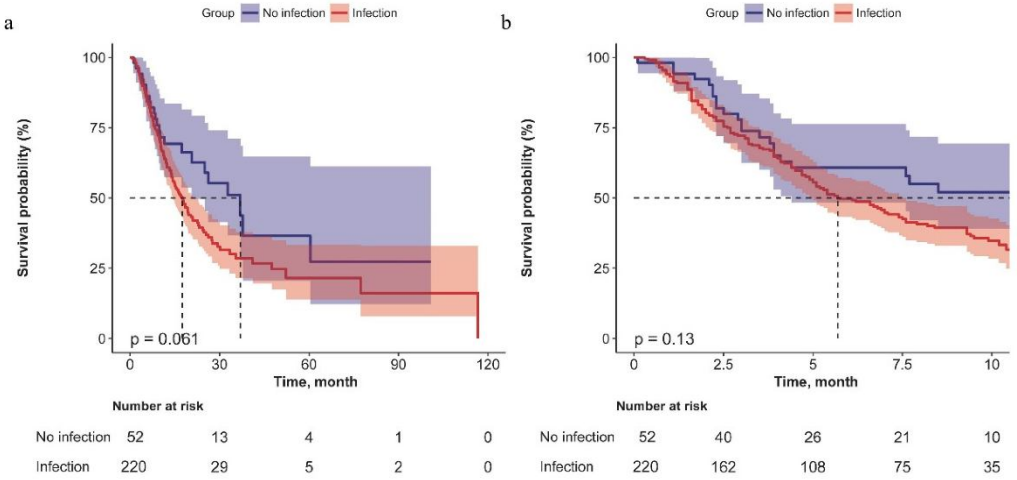

Figure 3. Kaplan–Meier Curves Depicting (a) Progression-Free Survival (PFS) and (b) Progression-Free Survival Post-COVID-19 (PFSC) in Lung Cancer Patients Affected by COVID-19**[141]**.

Table 1. Correlation between Lung Cancer Prognosis and COVID-19 infection**[141]**.

COVID-19	Model I		Model II		Model III	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
PFS						
No infection	1 (reference)		1 (reference)		1 (reference)	
Infection	1.52 (0.98~2.38)	0.063	3.28 (1.6~6.72)	0.001	3.39 (1.45~7.95)	0.005
PFSC						
No infection	1 (reference)		1 (reference)		1 (reference)	
Infection	1.41 (0.9~2.2)	0.13	2.83 (1.39~5.76)	0.004	3.84 (1.67~8.84)	0.002

Model I: Unadjusted; Model II: Adjusted for sex, age, pathology, vaccination, lung cancer treatment, treatment line, chest radiotherapy, anti-cancer therapy profile, underlying disease, smoking status, PS and smoking index; Model III: Adjusted for the variables in Model II plus COVID-19 treatment options. PFS: progression-free survival; PFSC: PFS after COVID-19.

A subgroup analysis stratified by lung cancer treatment type demonstrated that patients receiving targeted therapy who had a history of COVID-19 experienced shorter PFS (HR = 1.48, 95% CI: 0.84–2.61) and PFSC (HR = 1.34, 95% CI: 0.76–2.37) in univariate analysis compared to those without COVID-19; however, these results were not statistically significant. After adjusting for covariates, targeted therapy patients with COVID-19 showed significantly reduced PFS (HR = 5.96, 95% CI: 1.91–18.58) and PFSC (HR = 5.2, 95% CI: 1.65–16.38). For patients undergoing immunotherapy, no disease progression was observed among those without COVID-19 at the time of analysis, precluding meaningful statistical

comparisons. Importantly, no significant interactions were identified between lung cancer treatment modality and either PFS or PFSC in the subgroup analysis (all interaction p-values > 0.05). This study highlights the potential adverse impact of COVID-19 on the prognosis of lung cancer, with evidence of reduced PFS and PFSC in affected patients. However, statistical significance could have been more consistently observed. It is crucial that future research focuses on larger cohorts and mechanistic studies to fully understand the interplay between COVID-19 and lung cancer outcomes, particularly in various treatment modalities**[141]**.

5. SIGNALING MOLECULAR ASSOCIATION OF LUNG CANCER AND COVID-19 INFECTION

It has been proposed that there is a relationship between cancer and COVID-19 **(Figure 4) [40]**. Increased levels of different cytokines and changing expressions of ACE2, TMPRSS2, and plasminogen activator inhibitor-1 (PAI-1) may be highly important if they relate to a link between cancer and COVID-19. Flu-like symptoms and ARDS are two of the most common symptoms linked with severe COVID-19. SARS-CoV-2 infections and associated complications are extremely dangerous for lung cancer patients **[41-43]**.

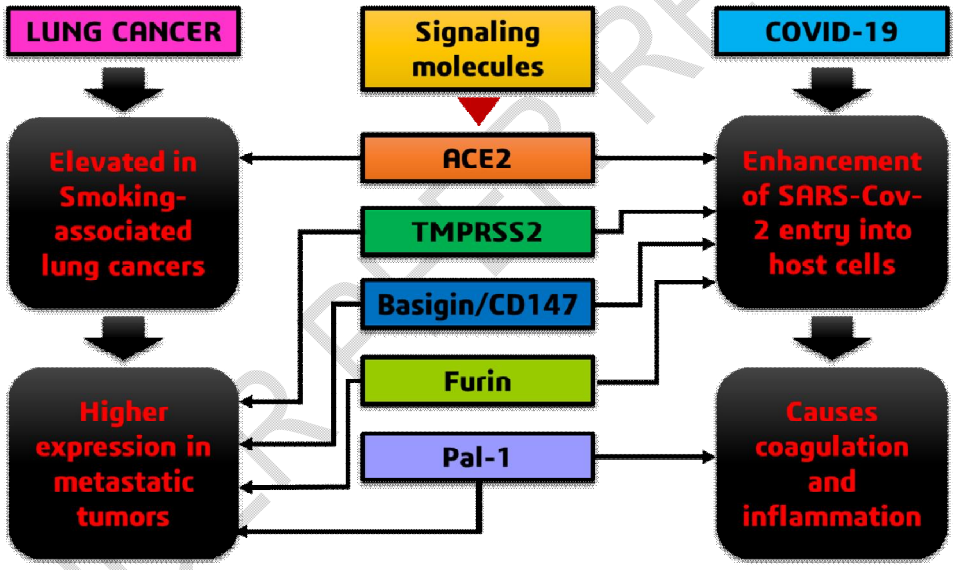

Figure 4. Signaling molecular factors linked with lung cancer and COVID-19. A huge number of specific cell surface proteins and enzymes play parallel roles in lung cancer progression and SARS-CoV-2 infection. Most of them seem to play a role in the entry of SARS-CoV-2 into host cells while also being reported to be elevated in metastatic lung cancers.

In contrast, lung cancer patients of all ages, subtypes, and clinical stages are substantially more vulnerable to SARS-CoV-2 infection **[43]**. Lung cancer patients are a vulnerable group to COVID-19, according to increasing statistics that show a high risk of hospitalization, the development of ARDS, and a high fatality rate **[44]**. Furthermore, SARS-CoV-2 has been found in the pleural fluid of a lung cancer patient **[45]**implying a yet-to-be-determined link between COVID-19 and lung cancer. In the following section, we'll summarize a few key genes shared by SARS-CoV-2 infection and lung cancer, which can help explain why the two diseases are linked.

5.1 COVID-19 AND LUNG CANCER ASSOCIATED ACE2 AND TMPRSS2 SIGNALING MOLECULES

ACE2 is indeed a cellular receptor for SARS-CoV-2 virus entry. Viral S proteins use the ACE2 receptor to integrate with the host cell membrane as well as enter by endocytosis, so this mechanism is controlled by type II transmembrane serine proteases (TTSPs), namely TMPRSS2 **[46]**. The lung is among the primary organs with high ACE2 levels, and ACE2 expression in both **[46]**lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) is much higher than in normal tissues **[47, 48]**. In airway epithelial cells, ACE2 is a human interferon-stimulated gene, and in lung epithelial cells, ACE2 and TMPRSS2 are co-expressed **[49, 50]**. Combining data shows that people who have a history of both tobacco smoking and lung cancer have a greater risk of SARS-CoV-2 infection than normal people because their lung cells produce more ACE2 and TMPRSS2.

TMPRSS2 is necessary for activating SARS-S CoV2's protein and also its proteolytic cleavage to infect host cells **[51]**. The TMPRSS2 protein is produced by the extensively conserved TMPRSS2 gene, and fusions of TMPRSS2 and ERG (ETS-related oncogene) are commonly found in malignancies **[52]**. In humans, TMPRSS2 is upregulated during development and has a direct association with age**[53]**. The function of these proteins in producing infection and the severity of the incidence of COVID-19 has been investigated by several researchers. Due to immunosuppression induced by cancer or chemotherapy, the risk of this viral infection is higher in cancer patients than in non-cancer individuals **[9, 54]**. The lungs are the predominant location of infection for this virus, so the highest effects are seen there **[55]**. As a result, lung cancer patients are considered to be at a greater risk of acquiring SARS-CoV-2 infection. In addition, immunohistochemical studies indicated a considerable ACE2 expression level increase in patients with lung cancer, particularly in the lower airways **[56]**. All such findings show that lung cancer patients are more susceptible to SARS-CoV-2 infection.

5.2 COVID-19 AND LUNG CANCER ASSOCIATED PAI-1 SIGNALING MOLECULES

In patients having recently confirmed lung cancer are hemostatic abnormalities, including enhanced coagulation but also fibrinolysis,have been observed **[57, 58]**. A study of advanced lung cancer patients identified high-density plasma fibrin networks indicated by enhanced coagulation activation **[58]**. Smoking was discovered to promote the plasma clot phenotype, as plasma cotinine levels were observed to correlate with fibrin concentration **[58]**. VTE is a common consequence of advanced-stage lung cancer therapy. Thromboprophylaxis is becoming more prominent in lung cancer patients **[59]**. The presence of D-Dimer in conjunction with thrombotic risk factors has increasingly encouraged doctors to prescribe anticoagulant medication to patients who have just had lung cancer surgery to lower the risk of VTE. Even though plasma from lung cancer patients has higher coagulation factors, hypercoagulability is unrelated to the histology of the malignancy **[60]**. The biomarker plasma plasminogen activator inhibitor 1 (PAI), which is involved in thrombotic, fibrinolytic, inflammatory, and metabolic signaling pathways, has become more well recognized as a biomarker of non-small cell lung cancer **[61]**. In COVID-19-related thrombosis, hypofibrinolysis and excessive thrombin production are also essential **[62]**. In hospitalized, symptomatic COVID-19 patients, plasma tissue plasminogen activator (tPA) and PAI-1 levels are high **[63, 64]**. As a result, PAI-1, like COVID-19, is a prevalent factor in lung cancer (Figure 4). It has also been observed that it promotes carcinogenesis in lung cancer **[65, 66]**. Considering that PAI-1 is an endogenous inhibitor of the oncogenic uPA/uPAR pathway **[67]**, its pro-carcinogenic activity is rather perplexing.

5.3 COVID-19 AND LUNG CANCER ASSOCIATED FURIN/PCSK3 AND BASIGIN (CD147) SIGNALING MOLECULES

In lung cancer, a variety of additional SARS-CoV-2-associated genes, such as basigin with paired basic amino acid cleaving enzyme (FURIN/PCSK3), have been studied **[68](Figure 4)**. Basigin, also called EMMPRIN or CD147, is up-regulated in lung cancer and has been associated with metastasis and poor prognosis survival **[69-71]**. It's a tumor cell surface glycoprotein that promotes the synthesis of matrix metalloproteinases and vascular endothelial growth factors, which are both recognized to be oncogenic and enhance cancer metastasis. Thus, this basigin family has been linked to lung cancer with bone metastasis **[72]**. Basigin is suggested to be associated with the SARS-CoV-2 spike protein, enhancing viral infection **[73]**, and making it a viable target for COVID-19 therapy **[74]**. Moreover, recent research challenging this hypothesis found no evidence of a basigin-SAR-CoV-2 spike protein relationship **[75]**. The field is quickly evolving, and additional research is required to thoroughly understand the importance of basigin in SARS-CoV-2 infection. Furin, another SARS-CoV-2-related gene, is another SARS-CoV-2-related gene. It has a well-established function. Furin is required for SARS-CoV-2 proteolytic activation and penetration into human airway cells. The SARS-CoV-2 infection that causes pathology depends on the cleavage site for furin in the spike protein **[76]**. This furin cleavage site has a unique insertion that allows only the SARS-CoV-2 spike protein to be cleaved, not the associated SARS-CoV-1 or even the MERS-CoV coronavirus. This evidence supports furin inhibition as a strategy for reducing SARS-CoV-2 infection, and a strategy has been identified as a result of this evidence. Furin is also being studied in lung cancer, where it is expressed in all malignancies, with exceptionally high levels in NSCLC, the most prevalent lung cancer subgroup, compared to small cell lung carcinomas. Furin levels are related to aggressive, metastatic malignancies, so furin inhibitors may inhibit lung cancer cells' development, proliferation, and metastasis, similar to how SARS-CoV-2 infection is inhibited by furin inhibitors **[77-79]**.

6. EPIGENETIC REGULATION OF LUNG CANCER ASSOCIATED COVID-19 INFECTION

Pathogenic injury (including that caused by environmental insults, oxidative stress, viruses, and bacteria) and remodeling of pulmonary tissues, which often results in chronic diseases such as asthma and COPD, are mediated by chromatin-modifying epigenetic mechanisms such as histone methylation and acetylation. Additionally, as explained previously, inflammation is directly linked to a variety of lung disorders, cancer, and COVID-19, and there has been a lot of interest in researching more about the mechanisms of inflammation, particularly the epigenetic mechanism of inflammation **[19]**. **(Figure 5)**.Inflammation can be controlled by a variety of epigenetic processes. Modulators like methylation and acetylation keep the balance between heterochromatin and euchromatin with flexible euchromatin, promoting gene transcriptional activity. Histone acetyltransferases (HATs) with other proteins having identical actions, including bromodomain-containing protein 4 (BRD4), acetylate histones, whereas histone deacetylases (HDACs) deacetylate them from histones. Methyltransferases are responsible for the methylation of DNA and histones, whereas demethylases are responsible for the demethylation. Finally, epigenetic modulation of inflammation is mediated by non-coding RNAs (both long non-coding RNAs (lncRNAs) and microRNAs (miRNAs). Induction of inflammation is characterized by the production of pro-inflammatory cytokines, chemokines, and chemokine receptors, as well as the mobilization of neutrophils and macrophages, an enhanced neutrophil-to-lymphocyte ratio (NLR), and coagulation. Lung damage and pulmonary disorders such as chronic obstructive pulmonary disease (COPD) and/or acute respiratory distress syndrome occur

from all of these symptoms (ARDS). This section summarizes the present understanding of the topic and concentrates on methylation, acetylation, and regulation through non-coding RNAs, the key researched epigenetic processes.

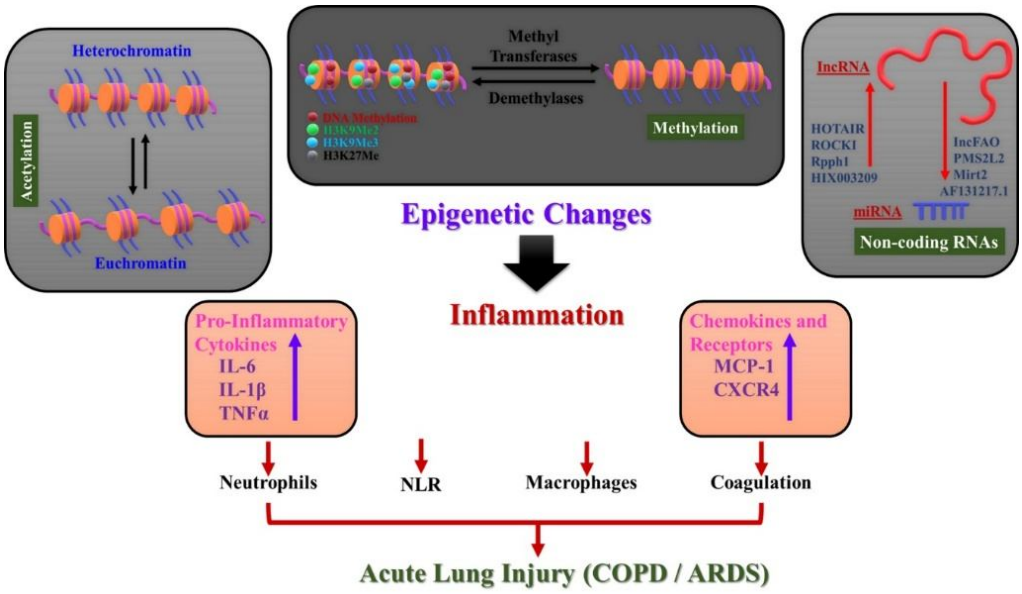

Figure 5: Inflammatory epigenetic regulation.

6.1 DNA METHYLATION REGULATING INFLAMMATORY GENES

During the development of asthma, COPD, and especially lung cancer, epigenetic gene regulation has already been found to modulate proinflammatory gene expression **[79]**. DNA methylation, histone methylation/acetylation, and non-coding RNAs are all involved in epigenetic modifications. DNA methylation is defined as the covalent attachment of a methyl group towards the 5′ carbon of cytosine (5mC) in a cytosine-phosphate-guanine (CpG) dinucleotide sequence, which is typically found in promoter regions, transcriptional gene sites, and regulatory gene sites **[80]**. DNA methyltransferases (DNMT) are enzymes that control DNA methylation. DNA methylation is commonly linked to transcriptional suppression, whereas demethylation is linked to gene transcriptional activation. Several oncogenes involved in lung cancer pathogenesis are induced or suppressed by changes in DNA stability (e.g., in CpG-rich areas adjacent to transcriptional sites) and histone methylation **[81]**. In malignant tissue but also lung cancer cell lines, research examining DNA methylation with the expression of inflammatory markers (IL-1, IL-6, and IL-8) found an indirect connection between DNA methylation and transcriptional activation among those inflammatory genes **[82]**.

A gene ontology study of DNA isolated from 1454 participants' peripheral blood found changed methylation in 330 out of 349 CpG sites, which regulated numerous genes, including alpha-1-antitrypsin (AAT), engaged in immunological but also inflammatory pathways that contribute to COPD pathogenesis **[83]**. Additionally, Bermingham et al. found that two of twenty-eight differentially methylated regions are significantly linked to the pathogenesis of COPD by adopting an 850 K Illumina EPIC array. Methylation significantly impacts the human lung epithelium, which is the largest environmentally exposed tissue. The degree of methylation differs based on the cell type. For example, most hypermethylated

CPGs were found within bronchial epithelial cells' promoter regions, while hypomethylated CPGs were found within asthmatic fibroblasts. The epigenetic alteration of immunological response has been identified by using DNA methylation patterns in peripheral blood cells among asthma patients. Several asthma therapy options involving dietary modifications have gained attention due to DNA CPG methylation alterations that are potentially more reversible than mutations **[84, 85]**. Therefore, methylation of genes impacts the transcription of genes encoding inflammation, but methylation also appears to be important in cancer and chronic respiratory disorders, including asthma and COPD.

6.2 ACETYLATION REGULATING INFLAMMATORY GENES

Another well-known epigenetic regulator of gene expression is acetylation. The introduction of an acetyl group to lysine (K) residues in histones and non-histone proteins has a significant effect on the control of gene expression. Proteins can be acetylated at two locations: the N-terminal acetylation site and the ε-amino group of lysines. Even though the first is a higher conventional co-translational modification, the second is a post-translational modification that has a variety of consequences, including the ability to influence protein function and half-life, as well as having a significant impact on the inflammatory reaction **[86]**. Histone acetyltransferases (HAT) regulate the addition of acetyl groups, whereas histone deacetylases (HDACs) control their removal; therefore, they are known as acetylation writers as well as erasers. Bromodomain as well as extra-terminal (BET) proteins, which can detect acetylated histones and are classified as detected acetylation, are rapidly becoming identified as inflammatory mediators. BETs were demonstrated to play an important role in the regulation of inflammatory genes, as well as cell proliferation and apoptosis. BRD2, BRD3, and BRD4 are BET proteins that control inflammatory gene expression by regulating the formation of histone acetylation-dependent chromatin complexes. BRD4 is a member of the BET family that not only detects histone acetylation but also includes the HAT characteristic, which is triggered through RelA activation. Through its direct interaction with NF-B, BRD4 plays a critical role in the regulation of inflammatory disorders **[86]**. BRD4 has also been observed to be enhanced in airway inflammation, which is linked to increased expression of IL-8 **[87]**. It was also linked to IL-1-enhanced human airway epithelial cell inflammation, TLR3-mediated airway remodeling, and virus-enhanced lung inflammation. The information-based data shows that the behavioral patterns of acetylation and deacetylation control the expression of genes linked to inflammation and other lung disorders.

6.3 NON-CODING RNAS REGULATING INFLAMMATORY GENES

In the last few years, there has been a lot of interest in the control of signaling pathways involving non-coding RNAs in a variety of human disorders **[88]**. Non-coding RNAs, such as long non-coding RNAs (lncRNAs) **[89-91]** and microRNAs, can be used to target and control inflammation andits immunological responses. Non-coding RNAs are one of the diverse RNA molecule groups, with newcomers constantly coming and being discovered. Individual non-coding RNAs control various signaling pathways, and their functions vary. A few of the lncRNAs that increase inflammation include HIX003209, ROCKI, Rpph1, and HOTAIR **[92]**, whereas others that decrease inflammation include lncFAO, Mirt2, PMS2L2, AF131217. miRNAs were observed to affect inflammation in terms of the exact mechanism by whichlncRNAs function. Non-coding RNAs can efficiently control inflammation as well as underlying mechanisms depending on this knowledge. MiRNAs that induce inflammation include miR-20a, miR-15b, miR-106a, miR-155, miR-421, and also miR-1307, whereas miRNAs that decrease inflammation include miR-10a, miR-24, miR-124,

miR-146a, miR-181, and miR-223. Based on this knowledge, non-coding RNAs have the ability to efficiently control inflammation as well as associated processes.

6.4 EPIGENETIC REGULATION OF INFLAMMATORY CYTOKINES ASSOCIATED LUNG CANCER AND COVID-19 INFECTION

6.4.1. INTERLEUKIN-6 (IL-6) ASSOCIATED LUNG CANCER AND COVID-19 INFECTION

The production of cytokines is primarily by activated immune cells in response to inflammatory stimuli. IL-6 is a significant pro-inflammatory cytokine affecting pulmonary and non-pulmonary disorders, which can be controlled epigenetically, according to previous publications and our current results. Numerous different molecular factors can be epigenetically regulated by IL-6. Its suppression of the methyltransferases DNMT1and DNMT3Bcan potentially affect the expression and functionality of various genes. It has been shown that IL-6 is confined to both direct and indirect epigenetic control. Because the suppressor of cytokine signaling-1 (SOCS-1) is involved in the negative control of IL-6, methylation, and subsequent SOCS-1 inhibition can activate IL-6 in cancer. IL-6, which is epigenetically controlled by miRNAs, may also control miRNAs. Let-7 and miR-149, for example, have been identified as targets that inhibit IL-6. Whenever IL-6 is overexpressed ectopically, it can suppress miR-370. The action of the methylation inhibitor 5-aza-2′-deoxycytidine on IL-6-mediated regulation of miR-370 indicates that methylation is involved. For example, IL-6 methylates and inhibits miR-142 similarly. IL-6 has been shown to significantly affect the methylation of several genesin addition to miRNA modulation. Loss of methylation at the promoters of cancer stem cell markers CD133 and CD44 can be induced by IL-6 **[93]**.

6.4.2 OTHER INFLAMMATORY CYTOKINES ASSOCIATED LUNG CANCER AND COVID-19 INFECTION

The role of proinflammatory cytokines in lung disease development has been shown in several investigations. Inflammatory/immune responses during pulmonary disorders are mediated by Th1/Th2 cell differentiation, which is controlled by the cytokines IL-4, IL-13, IL-5, and IFN-γ. IFN- is inhibited by the methyltransferase DNMT3a, which also methylates CpG-53 **[94]**. So, in the promoter regions of IL-4 and IL-13, CpG demethylation within DNase I hypersensitivity sites (DHS) regulates Th2 development. HATs and HDAC dysregulation have significantly affected IL-6 expression in a paraquat-induced lung fibrosis scenario. STAT-6 and its cytokines have been reported to be regulated by DNA methylation in the promoter region. CXCR4 and CXCL12 communicate directly to control cancer growth in multiple organs, particularly the lungs, and their activation has been linked to the demethylation of CXCR4 with hypermethylation of CXCL12 promoter regions **[95]**. According to a study on granulomatous lung disorders, methylation controls cytokine-cytokine receptor interaction, chemokine signaling, the JAK-STAT pathway, and cellular immunity. The development of lung cancer is regulated by the methylation of CpG islands within promoter regions, including IL-1, IL-6, and IL-8 genes. Histone acetylation and deacetylation instability also affect the production of inflammatory cytokines, affecting inflammatory gene expression**[96]**. Therefore, epigenetic control of inflammatory cytokines associated with the symptoms of developing lung cancer, pulmonary infections, and COVID-19 is supported by significant research results.

7. EPIGENETIC REGULATION MICRORNAS ASSOCIATED LUNG CANCER AND COVID-19 INFECTION

As previously suggested, multiple studies have found that miRNAs play a role in the control of inflammation. Considering these relationships among inflammation, lung cancer, and COVID-19, we evaluated the research for potential epigenetic interconnections. The functions of miRNAs in inflammation and lung cancer are well recognized, and new research shows that miRNAs may also contribute during COVID-19 infections. In contrast, a specific inappropriate expression of miRNAs characterizes immunological responses to several viral respiratory infections, especially COVID-19. Recent research has identified possible miRNAs that might target COVID-19-related host receptors, ACE2 as well as TMPRSS2, within SARS-CoV-2-infectable liver cancer cells Huh7 but also lung cancer cells Calu3, kidneys, cardiomyocytes, and even the hypothalamus. Deregulated miRNAs may potentially play a role in the significantly higher COVID-19-related mortality among older patients **[97, 98]**. This subsection highlights various miRNAs that were hypothesizedand identified to be associated with COVID-19 and lung cancer, including inflammation **(Table 2)**.

Table 2:miRNAs and their association with COVID-19, lung cancer, and inflammation.

miRNA	Role in Lung Cancer	SARS-CoV-2 target	Role in Inflammation
miR-15b	Promotes lung cancer growth and invasion **[99]**	Differentially expressed in Hamster lungs after SARS-C0V-2 infection **[100]**	Expression positively correlates with inflammation **[101]**
miR-29 family	Tumor suppressor with role in therapy resistance **[102, 103]**	Has 11 binding sites on the SARS-CoV-2 genome **[104]**	Anti-inflammatory in cancer and other diseases **[105, 106]**
miR-21	Oncogenic miRNA in lung cancer **[107, 108]**	Predicted to bind to human coronavirus RNA **[108]**	Regulator of inflammatory response **[109]**
miR-195	Tumor suppressor that associates with improved survival **[110]**	Differentially expressed in Hamster lungs after SARS-C0V-2 infection **[100]**	Promotes resolution of inflammation **[111]**
miR-98	Inhibits lung cancer proliferation and metastasis **[112]**	Targets TMPRSS2 in lung endothelial cells **[113]**	Expression negatively correlates with inflammatory cytokines **[114]**
miR-200 family	Tumor suppressor and negative regulators of EMT **[115, 116]**	miR-200c is predicted to regulate ACE2 in respiratory cells **[117]**	Members of this family have been reported to be pro-inflammatory **[118, 119]**as well as anti-inflammatory **[120, 121]**
miR-1207	Tumor suppressor with inhibitory effect on metastasis **[122]**	Targeted directly by SARS-CoV-2 RNA **[123]**	De-repression of its target CSF1 results in acute inflammatory response in COVID-19 **[123]**

miR-421	Overexpressed in lung cancer and associated with poor prognosis **[124]**	Regulates ACE2 **[125, 126]**	Aggravates inflammatory response in lung tissues **[126]**
miR-1307	Promotes lung cancer growth and proliferation **[127]**	Predicted to have the highest affinity for the SARS-CoV-2 genome among 1872 miRNAs **[128]**	Promotes inflammatory responses **[129]**

†References are specified by numbers in brackets. **EMT:** Epithelial-to-Mesenchymal Transition, **CSF1:** Colony Stimulating Factor 1.

MicroRNAs potentially target various genes of the infection-related SARS-CoV-2. Indeed, miR-98 has recently been identified as a TMPRSS2 target. Especially in the context of underlying endothelial cell dysfunction in the progression of COVID-19 infections, this work used lung endothelial cells to confirm TMPRSS2 targeting through miR-98 in this model system. High expression of miR-98 has already been observed to significantly lower pro-inflammatory cytokine levels and lung cancer proliferation and metastasis **[112]**.

8. CONCLUSIONS AND FUTURE PERSPECTIVES

The connection involving inflammation and many respiratory disorders with lung cancer appears instantly recognizable, and so does the relationship involving pulmonary diseases as well as lung cancer, including both respects of vulnerability to disease pathogenesis. The appearance of COVID-19 in recent years has resulted in significant efforts being dedicated to thoroughly studying this disease. Since the fatality rate linked with COVID-19 is low but not even proportional to other infections, its tremendous rate of infection has culminated in far more than 68 million cases globally, actually resulting in much more than 1.5 million fatalities at the time of this report in the first week of December 2020. Most existing evidence suggests a high connection between COVID-19 and pulmonary symptoms because COVID-19 patients frequently die as a consequence of major pulmonary problems. There is a direct correlation between COVID-19 and lung cancer because lung cancer patients are not just more prone to SARS-CoV-2 infections, but they also have a higher fatality rate. As detailed in this chapter, most genes involved in SARS-CoV-2 infection were also linked to carcinogenesis, suggesting the COVID-19-lung cancer linkage**[130-135]**.

The COVID-19 pandemic significantly impacted the management of lung cancer, necessitating healthcare facilities to adopt stringent protocols to minimize viral transmission while ensuring timely cancer treatment. These regulations included prioritizing telemedicine consultations, implementing screening measures for COVID-19 symptoms, and restructuring oncology services to accommodate urgent cases. Lung cancer patients faced limitations in accessing healthcare due to overwhelmed systems, travel restrictions, and fear of infection, often leading to delayed diagnosis and treatment. Immunosuppression from cancer therapies heightened their vulnerability to severe COVID-19 outcomes. Furthermore, potential drug interactions between COVID-19 therapeutics (e.g., remdesivir, corticosteroids) and lung cancer treatments such as tyrosine kinase inhibitors or immunotherapies posed clinical challenges**[136-140]**. Adjustments in treatment regimens, such as extending intervals between chemotherapy cycles or switching to oral medications, aimed to balance cancer care with infection risk mitigation. In this challenging landscape, the importance of multidisciplinary approaches cannot be overstated, providing reassurance and confidence in the face of this dual-threat scenario.

Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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