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**Review Article**

# The Association of COVID-19 Outbreak with Cancer Patients

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## ABSTRACT

SARS-CoV-2 was perceived in China which forms a pandemic within weeks and affected the whole world population. Unfortunately, some people who were already suffering from cancer were affected severely and had more disease severity. COVID-19 badly affected cancer diagnosis and treatment resulting in increased mortality rate. A major issue that cancer patients had to face was a lack of access to necessary health care. The "Renin-angiotensin-aldosterone system (RAAS)" plays a role in cancer development, it was observed that COVID-19 affects the functioning of RAAS by affecting the Angiotensin-Converting Enzyme -2 (ACE-2) receptor with the assistance of spike proteins to gain entrance into the cells. It was proved that the ACE 2 receptor is a major link between cancer and COVID-19. Cancer patients are very sensitive to COVID-19 due to "macrophages". Macrophages induce inflammatory responses in both cancer and COVID-19 patients. It was also observed that COVID-19 may create a microenvironment for cancer development by increasing the activation of macrophages, and neutrophils as well as causing the overproduction of proinflammatory cytokines.

## INTRODUCTION

Corona Virus-2 (SARS-CoV-2), the "acute respiratory syndrome" was first reported in "Wuhan", China, in December 2019, leading to a devastating outbreak of COVID-19. It became a pandemic in just a few weeks with over 30 million confirmed cases and over 0.2 million deaths, related to it. Around 15% of infected people had severe symptoms that demanded hospitalization and 3-10% of patients died because of Acute Respiratory Distress Syndrome (ARDS) [1-3]. Aside from an increased risk of contracting SARS-CoV-2, cancer patients also experienced more severe COVID-19 effects and/or have their prognosis impacted indirectly by delaying treatment [4]. A study was recently conducted with 105 cancer patients and 536 non-cancerous patients. According to these studies, cancer patients were found to have severe symptoms. Hematological, lungs, and stage IV cancer patients have shown the most severe symptoms and metastatic cancer patients had a increased death rate [5]. Another study shows that cancer patients (age around 63.1 years deteriorated quickly compared to younger cancer patients.) According to Desai et al., cancer patients have a two percent prevalence of COVID-19, and the patients who recently received chemotherapy or surgery had a75% highest risk of serious COVID-19 infection than COVID-19 patients without cancer, which had 43% chances [6]. In a study conducted by Zhang et al., 15 of 28 COVID-19 infected cancer patients experienced more severe COVID-19 signs and symptoms, and eight patients died. In these patients' lung, esophageal and breast cancer are the most common and he also shows that those patients who were on anti-cancer therapy developed more severe symptoms than those who were not on any cancer-related therapy [7].

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Mehta et al., showed that the death rate of COVID-19 infected patients was increasingly high in patients with lung cancer almost 55% with gastrointestinal cancer, almost 38% with pancreatic cancer, almost 67% with colorectal and 38% with gynecological cancer [8].
These studies are also shown graphically (Figure 1).

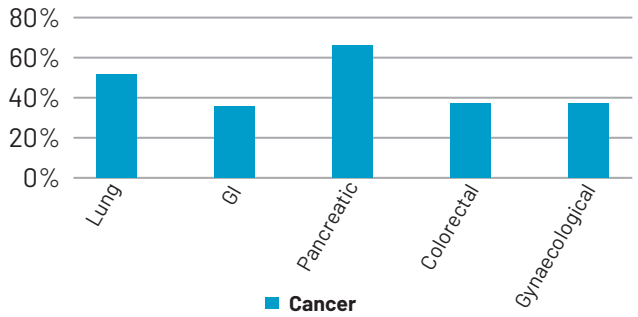


**Figure 1:** Death rate of COVID-19 in cancer patients

**Cancer Care:** Cancer care is also affected by COVID-19 because the routine checkups of cancer patients are highly delayed due to the pandemic as a reduction in routine checkups and mammography of healthy women also leads to ignorance of early symptoms of Breast Cancer which automatically leads to delayed diagnosis and treatment. The mortality rate of cancer also increases in the normal person [9]. Wang and Zhang said that the primary risk to cancer patients during the COVID-19 pandemic is slender access to medical care and the failure to get proper medical services promptly, especially in more hazardous epidemic areas like "Wuhan, China", where health staff and medical care facilities are in scarcity. Adverse effects of treatment in pulmonary cancer patients administered with the regulator of immune response (such as "severe myocarditis and pneumonitis") must be monitored by health care providers; such effects may harm the patients' endurance; thus, it is critical to investigate and treat such issues as soon as possible [10]. According to a newly published retrospective cohort analysis a study was conducted in which twenty-eight cancerous patients with COVID-19 were recruited from hospitals in "Wuhan", and this study states that patients infected with COVID-19 of cancer have more risk of poor clinical follow-ups, serious events, and impermanence. Therapy for cancer within 2weeks of COVID-19 detection was considered hazardous for serious events among these grave consequences that have been observed are acute respiratory distress syndrome which is at the risk of 28.6%, septic shock at three points six percent and acute myocardial infarction at 3.6% risk [7] (Figure 2).

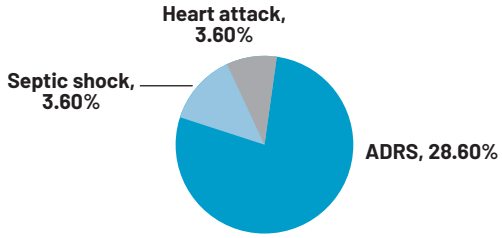


**Figure 2:** Risks that can be observed if cancer treatment is continued within 14 days of COVID-19 diagnosis

**Mode of Action:** In cancer biology, the "renin-angiotensin-aldosterone system" (RAAS) plays a role in the tumor cell modification and proliferation and cancer cells and it is also observed that COVID-19 affects the functioning of RAAS by using the angiotensin-converting enzyme -2 (ACE-2) Receptor to get entrance in the cell.

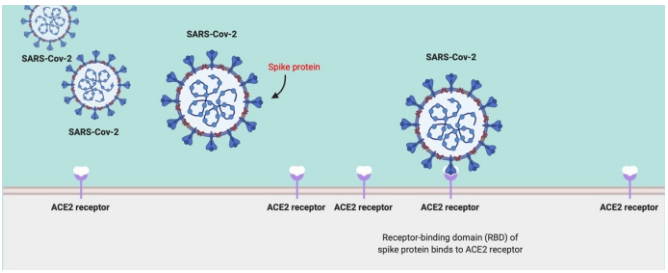


**Figure 3:** SARS-COV-2 binding to ACE receptor [11]

SARS-CoV2 when enters the body attaches with the ACE-2 receptor present on the exterior side of the host cell and causes diseases [12] (Figure 3). This receptor ACE-2 is found in the esophagus, nose, lungs, heart, stomach, colon, ileum, liver, and cornea, testis [13]. There is a protein called spike(S) protein that causes the virus attachment with the ACE-2, receptor, and these spike proteins are split by "host proteases such as transmembrane-protease-serine-2 (TMPRSS-2) cathepsin L, and furin." This S protein also helps in membrane breakdown which causes the excretion of viral RNA into the cytosol of the target cell [14,15].

**Spike protein:** The S protein, which is 180–200 kDa in size, is made up of two non-covalently linked subunits: an N-terminal subunit (S1) and a membrane-anchored subunit (S2) with separate roles. S is cleaved at the junction between the S1 and S2 subunits in many CoVs, although they remain non-covalently connected in the prefusion structure. As a result, when the virus interacts with the host cell, the S protein undergoes significant morphological changes, allowing the virus to connect to the host cell's membrane. The spikes are overspread with polysaccharide molecules to avoid detection by the host cell's immune system during entry [16,17]. 1273 AA is the length of the spike protein of SARS- CoV 2 and comprises of one peptide (amino acids 1–13). The "S1 subunit", also known as the N-terminal subunit contains 14-685 remnants of

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amino acid and 686–1273 residues make up the S2 subunit. In the "S1 subunit", there is the N-terminal sector and receptor-binding sector. The fusion-peptide, heptapeptide repeat sequence 1 (HR1), HR2, TM domain, and cytoplasm domain are all found in the "S2 subunit [18]. Visually it is observed that the viral fragments are encircled by a bulging, crown-shaped halo which is made up of S-protein trimers. According to the structural presentation of coronavirus S-protein monomers, the S1 forms the bulbous head and the S2 subunits from the stalk region [19]. Electron microscope with Cryo technique was used to analyze the atomic structure of the "SARS-CoV-2 trimeric S-protein" as well, which reveals the various configurations of the S-RBD sector in closed and open states, as well as their relevant activities [15,20]. In its native condition, the CoV S protein is an inactive precursor. During infection, target cell proteases such TMPRSS2 and furin split the S-protein into S1 and S2 subunits, which is essential for activating the membrane fusion sector after viral entry. The S-protein of "SARS-CoV-2" is broken into S1 and S2 subunits by proteases, similar to other coronaviruses, and the serine-protease "TMPRSS2" is employed as a primer [14,21,22]. In the infection S- proteins found on viral surfaces play an essential role. It is a "trimeric class-I TM glycoprotein", present in all domains of CoVs and other viruses including Ebola (Ebola virus glycoprotein), HIV (HIV glycoprotein 160, Env), influenza (influenza hemagglutinin, HA), paramyxovirus (paramyxovirus F), and paramyxovirus (paramyxovirus F). SARS-S CoV-2 is, similar to other corona-viruses, is also found to be a part of the identification of receptor, cell bonding, and fusion during viral infections. As a result, spike protein is only found in CoVs and similar viruses, and their primary target site is the ACE 2 receptor, which is abundant in cancer patients to prove this hypothesis scientists performing experiments [23-26].

**The Knot between COVID-19 and Cancer:** In the pathogenicity of the virus, the importance of the ACE-2 receptor was examined by inoculating a virus in a mice ACE-2 bearing transgenic mice. It was observed that ACE-2 infected mice lost weight and virus replication in the lungs as well as interstitial pneumonia, lymphocytes, and macrophage invasion in the alveolar interstitium were observed. There is also a macrophage buildup in the alveolar cavities so the viral antigens were found in the "bronchial and alveolar epithelial cells, also macrophages". On the second side, wild-type mice were not affected by the virus, because they do not contain human ACE-2 receptors. So, this experiment confirms the virulence of the virus only in those mice which contain human ACE-2 receptors [27]. According to a recent study, the appearance of ACE-2 in the lungs appears to rise with the years. People over the age of 60 years, as well as those with a weakened immune system, have been demonstrated to be particularly sensitive to COVID-19 infection, so this proves that ACE-2 expression increases in the lungs as the age increases. Moreover, ACE-2 expression is also found to be raised in the lungs of a patient who is a smoker or those patients who are suffering from smoking-related lung diseases i.e., lung cancer [28-31]. There is another relation between COVID-19 and cancer as is mentioned before host-protease TMPRSS-2, essential for "SARS CoV-2" to penetrate the target cell and isolate RNA of virus, these proteins are androgens regulatory genes that has been discovered to be significantly elevated in the prostate cancer as the "androgen's receptor" is found in "lungs and Prostate cells" it could play an important role in TMRSS-2 expression in these tissues [32]. A study found that "Prostate cancer patients" with "Androgen deprivation therapy" (ADT) experienced major depletion in COVID-19 patients compared to those patients who did not receive ADT or had other forms of cancer [33]. As in these studies, we observed a link between cancer and COVID-19 but there are some differences as well which are given below (Table 1),

| Cancer | COVID-19 |
|---|---|
| Series of genetic disease: genetic predisposition, DNA mutation | Single infectious disease |
| Environmentally influenced by: Inflammation, Microbiome | Environmentally influenced by ACE-2 receptor |
| Time duration is from month to year | Time duration from hours to days. |
| asymptomatic screening | Symptomatic screening |

**Table 1:** Difference between cancer and COVID-19 [34]

**Susceptibility of cancer patients toward COVID-19:** According to all these previous studies, a question arises how does a patient become more susceptible to COVID-19? The answer to this question would be "macrophages" because they play a key role in the erythrogenic responses related to cancer and COVID-19. In COVID-19 infection, macrophages M-1 is activated and this activation is linked to "macrophage activating syndrome (MAS), cytokine storm, lymphopenia, endothelial damage, and an increase in intravascular blood coagulation" whereas in cancer patients macrophages M-2 is activated which suppresses the immune response while promoting tumor development as a result of immune-suppression the response against virus is compromised making cancer patients more porn viral infection [35]. SARS -CoV-2 like many other onco-viruses induces inflammation however it is not confirmed that this virus contains tumorigenic properties. When COVID-19 occurs in a patient the level of cytokines (IL-6) is raised greatly. This increased level of IL-6 initiates the inflammatory indicating pathway causing a cytokine storm

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and this condition indicates that "SARS-CoV-2" may contain carcinogenic abilities. There is a previous study about coronavirus endoribonuclease Nsp-15, interacting with tumor suppressor retinoblastoma protein, due to this there is a downregulation of retinoblastoma protein causing the alteration of gene expression and causing an increase in cell division and growth [36,37].

**Association of COVID-19 with Cancer:** During recent studies, it was suggested that SAR-CoV-2 may provide a preferable environment that helps in the growth of cancer cells and it also initiates the formation of constituents that initiate inactive cancer. The human immune system during COVID-19 exhibits increased "activation of macrophages neutrophils and monocytes as well as overproduction of proinflammatory cytokines, and lymphopenia also occurs these activated neutrophils secrete a substance called neutrophil extracellular traps (NETs)". It is a webby structure of DNA and protein and it causes tissue injury. A recent study revealed increased neutrophil infiltration in the lungs of deceased COVID-19 patients during autopsy. Another study showed that NETs are involved in the generation of immune thrombosis in COVID-19 patients. It's suggested that NETs could reactivate dormant cancer cells in the COVID-19 inspired pro-inflammatory environment and increase the risk of cancer recurrence and metastasis [38]. From this discussion, it is indicated that the coronavirus may possess the ability to cause cancer and may promote carcinogenesis, but further research work is required to understand the tumorigenic activity of coronaviruses

## CONCLUSION

During recent years, the COVID-19 pandemic brings misery to mankind. Mankind is trying her best to eradicate this deadly virus and in this situation cancer patients suffer more because SARS-CoV-2 badly affects the health care systems which are dealing with cancer diagnosis and treatment. Scientists found a molecular knot between COVID-19 and cancer which includes "ACE-2 pro-inflammatory cytokines" and this evidence might help to cope with the fatal attack of COVID-19 and cancer but still more work is required. Scientific research communities must conduct detailed studies which will assist us to gain knowledge about the interaction between COVID-19 and cancer so that we can effectively treat those cancer patients that are affected by COVID-19.

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