RESEARCH ARTICLE OPEN ACCESS

Linkage Between COVID-19 and Cancer

Jidapa Tangnittayawong
Triam Udom Suksa School
Email: Jidapaaa2549@gmail.com

----------**********----------

Abstract:
COVID-19 is problematic to individuals nationwide, more than seven hundred billion cases have been reported globally. Several factors contribute to the risk of COVID-19 infection and cancer is one of them. As immunosuppression is the consequence of cancer itself and cancer treatments, there might be some correlation between these two conditions regarding the requirement of an immune response to tackle viral infection. Furthermore, it is interesting whether COVID-19 is a factor contributing to future initiation of cancer. If the association on this issue can be confirmed, prevention of cancer development must be emphasized. In this review, we collected the data and discussed the acquired information on various aspects of cancer and COVID-19.

Keywords **—cancer, COVID-19, Long COVID, coronavirus, SARS-CoV-2**

----------**********----------

I. INTRODUCTION

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus. Most patients experience mild to moderate symptoms. However, some factors have a role in increasing the severity of the disease. As a consequent, the patients become very ill and require intensive care. Factors that relate to the severity of outcomes include age and underlying symptoms like cardiovascular disease, diabetes, chronic respiratory disease, or cancer [1].

Since some cancer treatments weaken an ability to fight the infection and some types of cancer leads to immunocompromised, cancer patients are placed at a higher risk of COVID-19 [2]. Numerous reports indicated that cancer patients have a higher risk of infection [3],[4], a higher risk of experiencing severe symptoms [5],[6], and a higher risk of mortality [7]-[9]. Risk factors of long-term effects of COVID-19 on cancer patients have been analyzed. Furthermore, the possibility of COVID-19 infection leading to carcinogenesis has been found. However, more studies on this issue are still needed in order to confirm the causation.

This review article aims to provide an overview of the association between COVID-19 and cancer so that further studies can be conducted to confirm the recent information. Therefore, the treatments and measures can be developed in order to protect vulnerable patients.

II. BACKGROUND

Many studies have been conducted on specific parts of the correlation between COVID-19 and cancer, including the impact of COVID-19 on cancer patients, the severity of the disease on cancer patients compared to those without cancer, the risk of cancer patients developing Long COVID, etc. This study aims to analyze and combine the information in various aspects of those associations to find the relationship between COVID-19 and cancer.

III. RISK OF COVID-19 IN CANCER PATIENTS

The findings from the single-center retrospective study included 4,489 patients with laboratory-confirmed COVID-19 (71 of whom had cancer) at the hospital in Istanbul, revealed that patients with cancer were at a higher risk of COVID-19 infection (23.9%) compared to the patients without cancer (1.51%), accounted for approximately fifteenfold [3]. Another research conducted by L Zhang and colleagues on 28 COVID-19 cancer patients addressed that most of them were male [6]. This finding corresponds to the study in Italy, which suggested that males and the elderly are at a higher risk of getting COVID-19 [8]. The reason for males exhibiting a higher risk of COVID-19 might be that ACE 2 which is an important factor for viral entry is more widespread in males than in females [10].

The population-based study using the SNDS database: the French administrative health care database examined two groups of patients. The first group included 41,320 patients hospitalized in ICU due to SARS-CoV-2 (ICU-gr). Another group included 713,670 control individuals not hospitalized for SARS-CoV-2 (C-gr). These individuals were matched according to sex, year of birth, and French department, and were not diagnosed with cancer within the past 5 years. The cancer incidence was compared between the two groups during the follow-up period. It was found that, in ICU-gr, 2.2% were diagnosed with cancer after 1 month of contracting

COVID-19, compared to 1.5% in C-gr. ICU-gr had a 1.31 higher risk of being diagnosed with cancer after discharge from the hospital compared to C-gr. A similar trend was found when taking the risk of death into account. ICU-gr had a significantly higher risk of developing renal, hematological, colon, and lung cancer. For other malignancies, there are no significant differences between ICU-gr and C-gr. Among those with hematological cancer, ICU-gr had a substantially higher risk of developing leukemia, myeloma, and non-Hodgkin's lymphoma compared to the C-gr. According to the statistics, along with the studies confirming the immune dysfunction associated with renal and colon cancers [11]-[13] as well as the fact that any type of cancer may promote immune dysfunction [14], it is speculated that a severe SAS-CoV-2 infection may serve as an indicator for undiagnosed cancer [4].

IV. CLINICAL FEATURES IN PATIENTS WITHCOVID-19 AND CANCER

A. *Symptoms of COVID-19-Infected Cancer Patients*

Typically, cancer patients experience symptoms similar to those without cancer such as dry cough, fatigue, dyspnea, lymphopenia, and high levels of C-reactive protein. However, there are some particular symptoms such as anemia, and hypoproteinemia (due to nutrition deficiency). These conditions potentially lead to deteriorated immune response, which can lead to respiratory tract infection. Patients with lung cancer are prone to develop dyspnea much earlier compared to general patients and other cancer patients, and are more likely to have anoxia and accelerated progression of the disease [6].

B. *Complication*

The most common complication is Acute Respiratory Distress Syndrome (ARDS) (28.6%), Followed by Septic shock (3.6%), and Acute myocardial infarction (3.6%). The major causes of death are ARDS (12.5%), pulmonary embolism (12. 5%), septic shock (12.5%), and acute myocardial infarction (12.5%) [6].

C. *Risk factors of severe clinical features*

It is suggested from many studies that cancer patients have a higher risk of severe clinical events [5],[6]. Types of cancer relating to the increasing risk are Hematological cancer, including leukemia, myeloma, lymphoma, and lung cancer. The reasons are that malignant or dysfunctional plasma cells, lymphocytes, or white blood cells in general in hematologic malignancies have decreased immunologic function. Furthermore, patients with hematologic cancer are prone to the complications of serious infection, which can worsen the condition from COVID-19. Decreased lung function and severe infection in patients with lung cancer could contribute to a worse outcome [5]. Severity levels of clinical events also relate to the stage of cancer diagnosis, patients with early-stage cancer are found to have no significant differences in severity compared to the non-cancer group [6]. However, Stage IV cancer is common among those with severe symptoms. Among various cancer treatments, immunotherapy has the highest impact since it induces the release of a large amount of cytokines, which can be toxic to normal cells, including lung epithelial cells, and therefore lead to a more severe illness [5].

D. *Risk Factors of Mortality*

There appears to be a positive correlation between increasing age and a higher mortality rate [7]-[9]. This is due to various factors, including compromised immune responses, and the effects of congenital diseases. Moreover, types of tumors also result in varying severity levels of symptoms. Hematologic cancer patients (e.g.leukemia, lymphoma, multiple myeloma) tend to develop more serious symptoms and experience higher mortality rates. This kind of cancer weakens a patient's immune system; therefore, they are more susceptible to infection. Among a group of patients with solid tumors, those with lung cancer experience the highest death rate [5]. Another significant factor is the stage of cancer. According to the research, metastatic cancer patients exhibit a higher rate of mortality compared with others, 69.2% and 30.8%, respectively. Hypertension is the only complication that substantially affects mortality and is the most commonly encountered comorbidity (47.9%), followed by diabetes (35.2%) [3]. Courses of treatment also influence mortality rate, the group of patients acquiring immunotherapy exhibits the highest mortality rate. This is attributed to the fact that this approach is designed to enhance the immune cell's ability to detect cancer cells [15]. Activated Immune system from immunotherapy couples with immune responses triggered by coronavirus infection, the immune system becomes excessively active, subsequently leading to life-threatening events due to cytokine storm [16].

V. RISK OF DEVELOPING CANCER AFTER GETTING INFECTED WITH CORONAVIRUS

Immune cells release cytokines when they encounter coronavirus in order to communicate with other immune cells. However, if the amount of released cytokines is excessive, it will cause damage to the host's cells. There are various types of cytokines involved in this process and some of them can induce tumorigenesis. For example, IL-6 (Interleukin-6), apart from causing inflammation, it can also activate tumor growth and stimulate metastasis (The condition in which cancer cells spread to other organs) [17],[18].

The research conducted in Portugal mentioned the risk of being diagnosed with cancer after contracting COVID-19. The speculative mechanism was that it may have some correlation with pRb (retinoblastoma protein), which is an essential protein for cell division regulation and is a tumor suppressor protein [19].According to the findings, SARS-CoV-1 Endoribonuclease Nsp15 can cause a reduction in both quantity and quality of pRb. Nsp15 plays an important role in coronavirus pathogenesis. It was reported that this RNase is

responsible for the degradation of viral dsRNA intermediates, thus preventing host recognition [20],[21]. When NSP 15 binds to pRb, it becomes activated. Conversely, pRb becomes less effective. In normal conditions, the pRb function is to regulate the cell cycle. When its level is lower, the amount of cells in the S phase rises and promotes the expression of the promoter that is normally suppressed by pRb[21]. There is still no research on SARS-CoV-2 NSP 15, but from their similar structure (88% homology and identical quaternary structure) [22], it is expected to behave in the same direction. Another mechanism expected to be involved in cancer development following coronavirus infection is oxidative stress. Oxidative stress is recognized as both an initiator and promotor of carcinogenesis, through (i) direct mutagenic action of ROS promotion of DNA single and double-stranded breaks. (ii) DNA cross-linking, and inhibition of DNA mismatch repair mechanisms. (iii) through interactions with intracellular signaling pathways, ROS can promote proliferation, tissue invasion, angiogenesis, cancer cell survival, and chemoresistance. Oxidative stress is attributed to three main causes (i) the inclination of ACE 2 receptors. ACE 2 exhibits an important role in converting angiotensin II to Angiotensin 1,7 since a high level of Angiotensin II possibly leads to oxidative stress. (ii) increased amounts of immune cells responding to viral infection including macrophage which is a phagocytic cell, can also induce oxidative stress. (iii) The treatment using mechanical ventilation causes an increasing level of tidal volume (the amount of oxygen flowing through the lung in one breath) [23]and FiO2 [24](the concentration of oxygen that a person is inhaling); subsequently causing oxidative damage to the lung [25],[26].

VI. LONG COVID

A. *Term and Definition for Long COVID*

According to NICE (National Institute for Health and Care Excellence) and the Department of Health and Human Services (HHS) in collaboration with CDC and other partners, the term “long COVID” is defined as signs, symptoms, and conditions that are present in four weeks or more after the initial phase of infection [27],[28].

B. *Long COVID Patients with Cancer*

An increasing amount of studies observed COVID-19 sequelae in cancer patients. It was found that cancer patients develop similar symptoms to those without cancer. Furthermore, risk factors affecting the long-term effects of COVID-19 were analyzed. From the study observing 312 Covid-19 patients at MD Anderson Cancer Center for 14 months after confirmed positive testing, patients with solid tumours accounted for 75%, 60% of patients developed long covid within 7 to 14 months duration after getting infected. Female patients are found to have a higher risk of experiencing long covid [29]. This is in contrast with other research indicating long COVID symptoms are more common in males than females. Interestingly, the rate of hypertension is higher among those without Long COVID, while it is associated with a higher risk of severe complications in the acute phase of the disease. The rate of other comorbidities such as COPD and congestive heart failure were similar in both groups. Other risk factors, such as nationality, age, and oncological characteristics, including tumor stage and type are found to have no significant impact on developing long COVID conditions. Neutropenia, Lymphopenia, hypoxia, severe disease, multiorgan failure, various interventions, or hospital admission during acute COVID-19 disease were not associated with a higher risk of a long COVID. In contrast, one retrospective study suggested that Long COVID is more prevalent in patients aged 65 and older, patients with two or more comorbidities, and patients having a smoking history [30],[31].

Currently, there is no research on specific treatmentfor cancer patients with Long COVID. For those general patients, WHO has guided the way to alleviate symptoms. It is important to Assess for the red flag before the process of rehabilitation. In adults with post-COVID-19 condition, exertional desaturation and cardiac impairment following COVID-19 should be ruled out and managed before consideration of any physical exercise training. Post-exertional symptom exacerbation (PESE) and orthostatic intolerance are amenable to rehabilitation, but it should be adjusted for safety. In addition, types and forms of physical exercise should be adapted to the patient individually. A combination of education and skill training should be encouraged for patients to develop a great comprehension of what condition they are facing and their limits on specific tasks or activities. For example, patients with orthostatic intolerance need to understand individual triggers and avoid symptom-exacerbating factors. Physical exercises are important for patients with fatigue, orthostatic intolerance, arthralgia, and breathing impairment. This aims to enhance strength in individuals, prevent deconditioning, and regain the ability to do things. However, it has to be noted that physical training can be done only in the absence of PESE. Particular treatment for each symptom varies. For swallowing and olfactory impairment, swallowing exercises and olfactory training are important. Some symptoms may have to rely on drugs such as inflammatory drugs for arthralgia, and antidepressant drugs for alleviating depression [32].

VII. CONCLUSION

Cancer patients are more vulnerable to COVID-19 and more common in males and patients aged 65 and older. The symptoms faced by COVID-19 patients are similar to those found among general patients, such as dry cough, fatigue, dyspnea, lymphopenia, and high levels of C-reactive protein. The slight difference is that anemia and hypoproteinemia can be found in the cancer group. The most common complication and the primary cause of death is Acute Respiratory Distress Syndrome. Moreover, cancer patients are more likely to develop more severe symptoms. Mostly found among those

with hematological cancer due to the decreased immunologic function and complications of infection during SARS-CoV-2 infection. Apart from that, metastatic cancer and immunotherapy are found to have an association with a higher risk of severity. A similar trend is shown when focusing on the mortality rate.The risk factors and specific treatments for Long COVID have not yet reached a consensus. Ultimately, it is predicted that SARS-CoV-2 can potentially lead to further cancer development as the mechanism related to cancer initiation can be seen.

REFERENCES

[1] *Coronavirus disease (COVID-19)*. (n.d.). Retrieved from Organization, WorlHealth:https://www.who.int/health-topics/coronavirus#tab=tab_1

[2] prevention, C. f. (n.d.). *People with Certain Medical Conditions*. Retrieved from https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

[3] Erdal, G. S. (2021). The mortality rate of COVID-19 was high in cancer patients: a retrospective single-center study. *International journal of clinical oncology*, 826-834.

[4] Dugerdil, A. &. (2023). Severe SARS-CoV-2 infection as a marker of undiagnosed cancer: a population-based study. *nature*.

[5] Dai, M. L. (2020). Patients with Cancer Appear More Vulnerable to SARS-CoV-2: A Multicenter Study during the COVID-19 Outbreak. *Cancer discovery*, 783-791.

[6] al., L. Z. (2020). Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China.

[7] Sanchez-Pina, J. M.-S.-T. (2020). Clinical course and risk factors for mortality from COVID-19 in patients with haematological malignancies. *European journal of haematology*, 597–607.

[8] Rugge, M. Z. (2020). SARS-CoV-2 infection in the Italian Veneto region: adverse outcomes in patients with cancer. *Nat Cancer 1*, 784–788.

[9] Pathania, A. S. (2021). COVID-19 and Cancer Comorbidity: Therapeutic Opportunities and Challenges. *Theranostics*, 731-753.

[10] Kaseb, A. O. (2021). The Impact of Angiotensin-Converting Enzyme 2 (ACE2) Expression on the Incidence and Severity of COVID-19 Infection. *Pathogens, 10(3)*, 379.

[11] Böhm, M. e. (2001). Complex perioperative immuno-dysfunction in patients with renal cell carcinoma. *J. Urol. 166*, 831-836.

[12] Porta, C. e. (2007). Renal cell carcinoma-induced immunosuppression: An immunophenotypic study of lymphocyte subpopulations and circulating dendritic cells. *Anticancer Res. 27*, 165-173.

[13] Zhang, Y. R. (2020). Mechanisms of immunosuppression in colorectal cancer. *Cancers 12*, 3850.

[14] Kiessling, R. e. (1999). Tumor-induced immune dysfunction. *Cancer Immunol. Immunother. 48*, 353–362.

[15] Schuster, M. N. (2006). Cancer immunotherapy. *Biotechnology Journal, 1*, 138-147.

[16] Gibson, P. G. (2020). COVID-19 acute respiratory distress syndrome (ARDS): clinical features and differences from typical pre-COVID-19 ARDS. *The Medical journal of Australia*, 54–56.

[17] Briukhovetska, D. D. (2021). Interleukins in cancer: from biology to therapy. *Nat Rev Cancer 21*, 481-499.

[18] Lan, T. C. (2021). Inflammatory Cytokines in Cancer: Comprehensive Understanding and Clinical Progress in Gene Therapy. *Cells, 10(1)*, 100.

[19] Vélez-Cruz, R. &. (2017). The Retinoblastoma (RB) Tumor Suppressor: Pushing Back against Genome Instability on Multiple Fronts. *International journal of molecular sciences, 18(8)*, 1776.

[20] Chen, Y. H. (2022). Cellular origins of dsRNA, their recognition and consequences. *Nat Rev Mol Cell Biol 23*, 286-301.

[21] Bhardwaj, K. L. (2012). The coronavirus endoribonuclease Nsp15 interacts with retinoblastoma tumor suppressor protein. *Journal of virology, 86(8)*, 4294–4304.

[22] Kim Y, J. R. (n.d.). Crystal structure of Nsp15 endoribonuclease NendoU from SARS-CoV- Protein Sci n.d.

[23] Hallett S, T. F. (2023). Physiology, Tidal Volume. Treasure Island (FL): StatPearls Publishing.

[24] Fuentes S, C. Y. (2022). Fraction of Inspired Oxygen. Treasure Island (FL): StatPearls Publishing.

[25] Sun, Z. Y. (2015). Effects of mechanical ventilation with different tidal volume on oxidative stress and antioxidant in lung. *J Anesth 29*, 346-351.

[26] Miguel Alpalhão, J. A. (n.d.). Persistent SARS-CoV-2 infection and the risk for cancer. *Medical Hypotheses,Volume143,2020,109882,ISSN 0306-9877*.

[27] (NICE), N. I. (2022). *COVID-19 rapid guideline: managing the long-term effects of COVID-19*. Retrieved from National Institute for Health and Care excellent.

[28] prevention, C. f. (2023). *Long COVID*. Retrieved from https://www.cdc.gov/coronavirus/2019-ncov/long-termeffects/index.html

[29] Dagher, H. C.-G. (2023). Long COVID in cancer patients: preponderance of symptoms in majority of patients over long time period. *eLife, 12, e81182*.

[30] David J Pinato, P. P. (2021). Prevalence and impact of COVID-19 sequelae on treatment and survival of patients with cancer who recovered from SARS-CoV-2 infection: evidence from the OnCovid retrospective, multicentre registry study. *The Lancet Oncology*.

[31] Monroy-Iglesias, M. J.-L. (2022). Long-term effects of COVID-19 on cancer patients: the experience from Guy's Cancer Centre. *Future oncology (London, England), 18(32)*, 3585–3594.

[32] Organization, W. H. (2023). Clinical management of COVID-19: Living guideline.

