Exploring the Complex Interactions Between COVID-19, Oxidative Stress, and Cancer Susceptibility

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Abstract

The emergence of COVID-19 as a global pandemic has posed significant challenges, impacting millions worldwide and spurring urgent research into its pathogenesis and associated complications. This review examines the complex relationship between COVID-19, oxidative stress, and cancer susceptibility. COVID-19, caused by SARS-CoV-2, affects multiple organ systems and presents a wide range of symptoms with serious consequences. Oxidative stress, characterized by an imbalance between prooxidants and antioxidants, plays a crucial role in the pathogenesis of COVID-19, potentially worsening disease severity and influencing patient outcomes. The interaction between oxidative stress, inflammation, and COVID-19 progression is intricate, with oxidative stress biomarkers emerging as key contributors to disease severity. Furthermore, post-COVID-19 complications, including increased cancer risks, highlight the long-term effects of SARS-CoV-2 infection. Understanding the complex dynamics of oxidative stress, inflammation, and cancer susceptibility in the context of COVID-19 is essential for developing comprehensive healthcare strategies and reducing the global disease burden.

Significance | Oxidative stress in COVID-19 causes disease severity, induces inflammation, and may increase post-infection cancer risks through DNA damage.

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1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) triggered COVID-19 which first appeared in 2019 thus ignite a worldwide pandemic. The World Health Organization (WHO) legitimately declared COVID-19 as a pandemic that resulted to a significant increase in the worldwide illness burden (Freeman et al., 2022). SARS-CoV-2 impacts various body cells especially the respiratory tract. Within two weeks of infection, COVID-19 symptoms such as cough, weariness, and respiratory problems appear, with millions of people infected in over 235 countries. Transmission occurs through respiratory droplets, necessitating various testing methods like RT-PCR for diagnosis. COVID-19 damages the heart, causes neurological issues, and triggers immunological responses, among other effects on other bodily systems.

Inflammation and oxidative stress are related in COVID-19. Oxidative stress causes an overabundance of reactive oxygen species (ROS), which can trigger inflammatory pathways and exacerbate the inflammatory response. On the other hand, inflammation can intensify the creation of ROS, resulting in a vicious cycle that worsens the disease and causes more tissue damage. The virus interacts with ACE2 receptors, potentially impacting the central nervous system and cardiovascular tissues, while immune responses show signs of a cytokine storm. Individuals experience a range of physical and psychological symptoms, termed "sequelae" or "post-COVID-19 syndrome". Extensive studies highlight oxidative stress biomarkers in SARS-CoV-2, influencing COVID-19's pathogenesis. This review explores SARS-CoV-2's molecular

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pathogenesis, connecting it to oxidative stress, inflammation, and post-COVID-19 cancer risks.

2. The effect of Oxidative Stress on Pathogenesis COVID-19

Oxidative stress has a major effect on COVID-19 development, which in turn affects the severity and course of the disease. Severe cases exhibit crucial biomarkers like lymphopenia, abnormal iron balance, and reduced circulating immune cells (Terpos et al., 2020; Bellmann-Weiler et al., 2020). Recent evidence highlights a strong correlation between oxidative stress and COVID-19 severity, revealing the intricate relationship between physiological factors and disease progression (Williamson et al., 2020; Delgado-Roche & Mesta, 2020). Specific risk factors such as male gender, low socioeconomic status, hyperglycemia, and obesity heighten oxidative stress levels, exacerbating COVID-19 severity (Williamson et al., 2020; Delgado-Roche & Mesta, 2020). Comprehending these variables is crucial in tailoring focused treatment approaches to mitigate oxidative stress and enhance patient outcomes.

In COVID-19 progression, the SARS-CoV-2 virus attacks type II pneumocytes rich in mitochondria, triggering oxidative stress and potentially inducing respiratory distress and acute respiratory distress syndrome (ARDS) (Chernyak et al., 2020). Preserving mitochondrial integrity, particularly in respiratory distress and in situations requiring oxygen treatment becomes crucial (Chernyak et al., 2020). Non-structured viral proteins like the coronavirus 3a protein and inflammatory pathways like the NLRP3 inflammasome increase oxidative stress by raising mitochondrial ROS levels (Chen et al., 2019; Xu et al., 2020). ROS are essential for many biological functions, including the generation of mitochondrial energy, host defence, cellular signalling, and gene expression regulation (Gain et al., 2023). Excessive ROS production will cause imbalance of oxidation condition and resulted in negative effects towards cells and tissues functions.

Elevated production of reactive oxygen species (ROS) is a significant factor in the increased expression of adhesion molecules and heightened endothelial permeability, which are dependent on tumor necrosis factor (TNF). The precise mechanism by which TNF induces ROS generation is not yet fully understood. An efficient system of antioxidants, which are molecules able to neutralize ROS which avoid oxidative stress, controls the generation of ROS under physiological conditions (Fodor et al., 2021). Natural enzyme antioxidants found in tissues, such as glutathione peroxidase, catalase, and superoxide dismutase (SOD), are crucial in the process of converting reactive oxygen species (ROS) into oxygen and water.

Immune complex formation involving IgG antibodies and the SARS-CoV-2 S protein induces hyper-inflammatory reactions in macrophages, further contributing to oxidative stress (Hoepel et al., 2020). Inflammatory responses from immune cells like monocytes and macrophages contribute to oxidative stress by releasing cytokines, worsening severe symptoms (Merad Martin, 2020; Wieczfinska et al., 2022). Understanding these molecular interactions is crucial for developing targeted therapeutic strategies to modulate oxidative stress in COVID-19 patients. Further research is imperative to refine therapeutic strategies combating the complex interplay between oxidative stress and COVID-19 pathogenesis.

Anemia and abnormal iron homeostasis are frequent among hospitalized COVID-19 patients, with initial anemia and usually have higher mortality rates (Bellmann-Weiler et al., 2020). SARS-CoV-2 attacks hemoglobin (Hb) groups in the red blood cells result in the release of free Fe (III) ions from the heme groups into the bloodstream, which raises ferritin levels. The virus-mediated hemoglobinopathy and iron dysmetabolism may be responsible for the clinical symptoms that were emphasized during COVID-19, such as mitochondrial damage, oxidative stress, ferroptosis, and lipid peroxidation (Beltrán-García et al., 2020). Early in the illness, lymphocyte counts are normal or slightly reduced, substantial lymphopenia develops later, coinciding with worsening clinical status and the onset of a cytokine storm (Terpos et al., 2020). Severe illness significantly decreases circulating CD4+, CD8+, B cells, and natural killer (NK) cells, while plasma cells increase notably.

Since oxidative stress is consistently triggered by viral pneumonia which may exacerbate the severity of the disease, it is imperative to understand how oxidative stress biomarkers affects SARS-CoV-2 pathogenesis. The coronaviruses are a broad class of viruses that include the alpha, beta, gamma, and delta subfamilies. Nevertheless, the most severe morbidity and mortality are caused by beta-coronaviruses, which belongs to SARS-CoV-2 (Forcados et al., 2021).

Factors like male gender, low socioeconomic status, hyperglycemia, and obesity have a high association with the elevation of oxidative stress; thus, they are significant risk factors for COVID-19 severity. Increased oxidative stress may worsen COVID-19 severity, as the virus triggers viral pneumonia, leading to excessive immunological responses and associated oxidative stress. Preserving mitochondrial integrity and understanding molecular interactions driving oxidative stress are critical for developing targeted therapeutic interventions (Figure 1).

Immune cells release harmful substances like reactive oxygen species (ROS), which cause tissue damage. Proinflammatory cytokines such as TNF-α and IL-1 further worsen the situation by promoting iron uptake, thereby increasing oxidative stress. This cascade of events underscores the intricate relationship between inflammation, oxidative stress, and tissue damage in COVID-19.

3. Post-COVID-19 infection and Cancer Risk

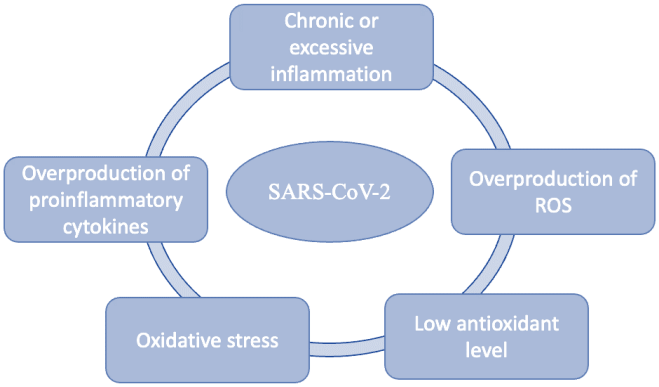

Figure 1. In SARS-CoV-2 infection, excessive inflammation initiates a critical molecular cycle.

Concerns are raised by the rising rate of cancer after COVID-19 because of uncertainties surrounding heightened susceptibility, viral exposure, and the scarcity of data. COVID-19 respiratory infections are linked to oxidative stress and a disruption in redox balance. The cytokine storm creates a proinflammatory environment strongly associated with severe tissue damage and fatal outcomes in COVID-19 patients. The correlation between inflammation and oxidative stress is well established, and oxidative stress is commonly characterized by an imbalance that favors prooxidants over antioxidants, leading to cellular damage (Delgado-Roche & Mesta, 2020). Oxidative stress plays a critical role in innate immunity and the antiviral immune response. Despite a significant correlation between oxidative stress indicators and the severity of various viral infections such as hepatitis C (HCV), clinical data on SARS-CoV are still scarce

However, preclinical evidence suggests a significant role for excessive ROS production and diminished antioxidant defences in SARS-CoV infection and the development of respiratory illnesses. Elevated reactive oxygen species (ROS) levels and weakened antioxidant defences are seen in experimental animal models of severe acute respiratory syndrome following SARS-CoV infection (Delgado-Roche & Mesta, 2020). Studies by Lin et al. indicate that the SARS-CoV protease 3CLpro significantly increases ROS formation in HL-CZ cells, contributing to cell death. Activation of the NF-kB-dependent reporter gene by SARS-CoV 3CLpro, associated with increased ROS levels, suggests a significant role of ROS-activated NF-kB signalling in SARS-CoV pathogenesis. Additionally, the 3a protein of SARS-CoV has been linked to the stimulation of mitochondrial cell death pathways, involving Bax oligomerization and increased p53 levels, dependent on p38 MAPK activation. The activation of mitogen-activated protein kinase (MAPK) signalling pathways, known to respond to oxidative stress, DNA damage, carcinogenic stimuli, and viral infections, is observed in SARS-CoV-infected cells, likely contributing to the host cell response to viral infection (Mehandru & Merad, 2022). This suggests that MAPK signalling pathway activation is a common feature in SARS-CoV-infected cells, potentially influencing the host cell response to viral infection.

Determining vaccination priorities and understanding the interaction between cancer and COVID-19 require thorough investigation, connecting cohorts via population registries or comprehensive medical data, including vaccination details. More research is necessary to understand these characteristics in the context of known and new variants of COVID-19, given the diversity in risk based on cancer type, time since diagnosis, and cancer therapy. Age, gender, comorbidities, and the extent of SARS-CoV-2 exposure should be taken into account to evaluate variations in biological susceptibility. Disparate reactions to COVID-19 vaccinations may arise from differences in immune competency between cancer types and treatments (Song et al., 2021). Study from (Addeo et al., 2021) stated immunosuppressive conditions linked to specific cancer types and cancer therapies can impede the development of acquired immunity to vaccinations. Thus, cancer types identification is essential before introducing vaccines towards patients to avoid any adverse effects.

The intricate process of cancer development involves cellular and molecular alterations influenced by both endogenous and exogenous factors. Oxidative DNA damage is widely acknowledged as a catalyst for cancer development, precipitating chromosomal abnormalities and activation of oncogenes. The association between oxidative stress and cancer pathogenesis is apparent, with various DNA modifications induced by oxidative stress contributing to tumorigenesis. Factors like tobacco usage, environmental pollutants, and chronic inflammation contribute to oxidative DNA damage, influencing tumor initiation. Lifestyle decisions that cause oxidative stress, such eating a lot of fat in food, can have a big impact on the cancer development. The pathophysiological mechanisms underlying significant tissue damage in COVID-19 patients are impacted by respiratory viral infections, which are associated with oxidative stress and a disturbance in redox balance.

A proinflammatory environment caused by the cytokine storm seen in COVID-19 is highly associated with significant tissue damage and unfavourable patient outcomes. The intricate interplay between inflammation and oxidative stress is well-established, with oxidative stress characterized by an imbalance favouring prooxidants over antioxidants, resulting in cellular harm. Early identification is perhaps the most effective intervention in cancer care like countless screening tests are recommended for at-risk populations due to age, family history, genetic testing, or personal medical history as part of standard care (Allen, 2022). Comprehending the intricate relationship between COVID-19, cancer, and oxidative stress necessitates a comprehensive approach that considers vaccination priorities, risk factors, and the complex biology of cancer development. Detailed investigation of these aspects are essential to develop global strategies to combat COVID-19 and cancer.

4. **Conclusion**

In summary, the onset of cancer subsequent COVID-19 presents noteworthy concerns, given uncertainties regarding increased vulnerability, viral exposure, and limited information. Prioritizing vaccination strategies for cancer patients has been influenced by their exposure to SARS-CoV-2 and the severity of COVID-19, highlighting the need for their prioritized protection. It is essential to conduct thorough research into the different cancer risks, including cancer type, time since diagnosis, and treatment options. Age, gender, and existing health conditions should be considered

with necessary adjustments made based on levels of exposure to SARS-CoV-2. Prolonged COVID-19 may entail persistent oxidative stress and inflammation, which may elevate chronic health problems, such as cancer. Oxidative stress-induced DNA damage, influenced by factors such as tobacco use and inflammatory conditions, plays a central role in cancer development, underscoring the intricate connection between COVID-19 and subsequent cancer complications. It is essential to conduct comprehensive research to refine therapeutic approaches amidst the complex interplay of oxidative stress and COVID-19 pathogenesis.

Author contributions

N.J., R.B.S.M.N.M., and N.H.A.M. contributed equally to this work. N.J. conceived the study and designed the experiment. R.B.S.M.N.M. conducted the data analysis and interpretation. N.H.A.M. provided critical revisions to the manuscript and assisted with data collection. All authors reviewed and approved the final version of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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