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Review

Impact of SARS-CoV-2 on Oncogenesis: A Deep Dive into the COVID-19 and Cancer Nexus

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Abstract

Background: The COVID-19 pandemic, triggered by the SARS-CoV-2 virus, has posed significant global health challenges, notably affecting individuals with pre-existing conditions like cancer. This review aims to provide an overview of current evidence regarding the bidirectional relationship between COVID-19 and cancer, focusing on potential mechanisms driving this association.

Search Strategy: A systematic search of the PubMed, Scopus, and Web of Science databases was conducted to identify studies published between January 2020 and March 2024. Articles were selected based on their relevance to the topic and adherence to rigorous methodological standards.

Results: Research indicates a complex interaction between COVID-19 and cancer, with clinical data highlighting variations in cancer diagnosis, prognosis, and treatment efficacy during SARS-CoV-2 infection. Mechanistic studies suggest that immune system dysregulation, chronic inflammation, and possible viral-induced cellular changes may contribute to cancer progression. Additionally, the pandemic has disrupted cancer care, causing delays in diagnosis and treatment, exacerbating existing healthcare disparities, and negatively affecting patient outcomes.

Conclusions: SARS-CoV-2 impacts cancer progression through a combination of direct and indirect mechanisms. Future studies should focus on identifying vulnerable cancer patient populations, clarifying molecular pathways connecting COVID-19 and cancer progression, and developing tailored therapeutic approaches to mitigate these risks.

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1. INTRODUCTION

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in late 2019, which triggered the coronavirus disease 2019 (COVID-19) pandemic [1], has brought about profound changes in global health. As reported by the World Health Organization, by December 2023, the virus had infected nearly 772 million individuals and caused over 6.9 million deaths [2][3]. Coronaviruses, including SARS-CoV-2, are enveloped viruses characterized by a large, single-stranded, positive-sense RNA genome [1]. SARS-CoV-2 induces respiratory conditions that can range from mild to critical, with complications including chronic obstructive pulmonary disease (COPD), pneumonia, lung cancer, and, in severe cases, death. Transmission primarily occurs via respiratory droplets and aerosols, although it can also be facilitated through contact with contaminated surfaces or objects [4].

In recent years, various studies have highlighted the intricate connection between viral infections and oncogenesis, with viruses such as Epstein-Barr virus (EBV), human papillomavirus (HPV), and hepatitis B virus (HBV) being associated with the development of various malignancies [5][6][7]. Drawing parallels from these well-established associations, researchers have begun to investigate the potential oncogenic properties of SARS-CoV-2, particularly in individuals with pre-existing cancer or those undergoing cancer therapy. There has been significant research done to uncover the potential mechanisms that link SARS-CoV-2 infection to the onset of cancer [8]. Bogomolets et al stated that COVID-19 may have direct or indirect effects on the development of cancer [9]. One area of COVID-19 and cancer exploration involves the virus's ability to interfere with cellular pathways responsible for regulating cell proliferation, apoptosis and immune surveillance [10]. These irregularities can set the stage for the development and progression of cancer. Moreover, the systemic inflammation and immune dysregulation caused by severe COVID-19 infection can create a microenvironment that is conducive to tumor growth and metastasis [11]. The virus can potentially damage the body's immune system, making it easier for cancer cells to grow and spread. These suggest that individuals who have contacted COVID-19 may have a higher risk of developing cancer in the future. Studies have shown that patients with cancer infected with SARS-CoV-2 experience a notably higher mortality rate compared to those without cancer (11.4%-35.5% vs. 3.8%-8.5%) [12]. Furthermore, the COVID-19 pandemic has presented distinct challenges to the delivery of cancer care, including disruptions in screening programs, delays in diagnosis, modifications in treatment methods, and increased susceptibility to infection among cancer patients due to their immunocompromised state [13][14][15]. These unprecedented circumstances have prompted the scientific community to investigate the broader implications of SARS-CoV-2 infection on the oncological landscape, encompassing aspects of cancer biology, clinical management, and public health policies. It is essential to investigate the connection between SARS-CoV-2 infection and oncogenesis to determine the potential cancer risk among COVID-19 patients and survivors. Knowing how viral infections like SARS-CoV-2 can affect cancer development or progression can help medical researchers to establish the development of targeted cancer prevention strategies, and personalized management strategies for individuals who have a history of COVID-19 [10][8]. Knowledge of the nexus between SARS-CoV-2 and cancer also helps patients, healthcare providers, and communities to make informed decisions regarding cancer prevention, screening, and treatment [16].

The existing knowledge gaps and uncertainties that concern the nexus between COVID-19 and oncogenesis include a poor and limited understanding of the basic biological mechanisms that link COVID-19 and oncogenesis [18], and the differences in cancer subtypes and the diversity among COVID-19 patients, which leads to presentation of a wide range of symptoms, severity, and outcomes [16]. As a title of example, Ground Glass Opacities in COVID-19 may reveal higher risk of lung cancer [19]. Besides, apart from lung cancer, SARS-CoV-2 elevates the risk of breast and gastrointestinal cancers and it was proved by Mitrofanova et al that it increases the risk of heart tumors [20]. In another perspective, this virus can also induce the reactivation of the oncogenic herpes viruses and the cancers such as Kaposi Sarcoma [21]. More research is needed to further understand the molecular pathways by which this deadly virus, SARS-CoV-2 may contribute to the development of cancer. This study aims to analyze the global impact of SARS-CoV-2 on oncogenesis and to explore patterns, trends, and commonalities in cancer occurrences among individuals with a history of COVID-19.

2. EPIDEMIOLOGICAL INSIGHTS INTO THE ASSOCIATION BETWEEN COVID-19 AND CANCER

Amidst the global COVID-19 pandemic, researchers have explored into epidemiological studies to clarify the association between SARS-CoV-2 infection and cancer.

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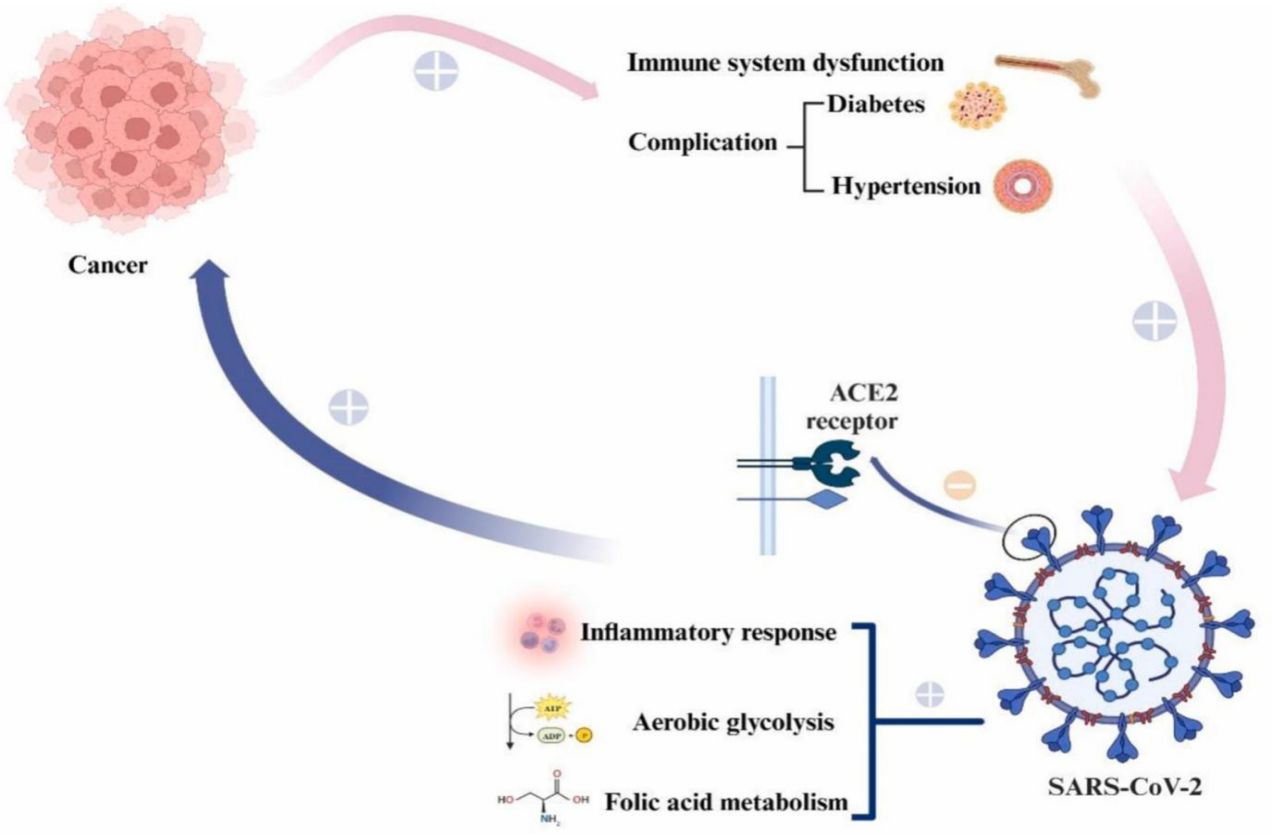

Figure 1. Relationship between cancer and COVID-19 [17]. Cancer weakens the body's immune system and can lead to complications like diabetes and hypertension, which heighten the risk of contracting SARS-CoV-2. In turn, SARS-CoV-2 infection may accelerate cancer progression by triggering inflammation and disrupting processes such as aerobic glycolysis and folate metabolism. Additionally, the reduced activity of ACE2 receptors due to SARS-CoV-2 infection plays a role in influencing cancer progression.

These studies have shed light on the increased vulnerability of cancer patients to COVID-19 and its effects on cancer diagnosis, prognosis, and mortality. Early investigations by Robilotti et al. (2020) [22] revealed that patients with cancer are at increased risk of experiencing severe COVID-19 disease manifestations, including higher rates of hospitalization and mortality. Similarly, Diao et al. (2020) [23] conducted a multicenter study that demonstrated heightened vulnerability to SARS-CoV-2 among cancer patients, emphasizing the importance of tailored interventions for this population. Moreover, Miyashita et al. (2020) [24] reported a poorer prognosis of COVID-19 among cancer patients in New York City, underscoring the need for enhanced surveillance and management strategies in regions heavily impacted by the pandemic.

In a large cohort study by Kuderer et al. (2020) [25], the Clinical Impact of COVID-19 on Cancer Patients (CCC19) consortium identified several prognostic factors linked with adverse outcomes in cancer patients infected with SARS-CoV-2. Key factors such as advanced age, male gender, comorbidities, and active cancer treatment were linked with higher mortality, highlighting the importance of risk stratification and clinical decision-making in this population. Furthermore, Wang et al. (2020) [26] explored the impact of the COVID-19 pandemic on cancer care delivery in the United States, revealing delays in cancer diagnosis and treatment initiation among elderly patients. These delays were attributed to disruptions in healthcare services, resource allocation, and patient reluctance to seek medical attention amidst the pandemic, emphasizing the need for proactive measures to mitigate the long-term consequences of delayed cancer care.

3. BIOLOGICAL MECHANISMS UNDERLYING THE POTENTIAL ONCOGENICITY OF SARS-COV-2

While the primary impact of SARS-CoV-2 is respiratory, emerging evidence suggests potential oncogenic implications of the virus beyond its respiratory

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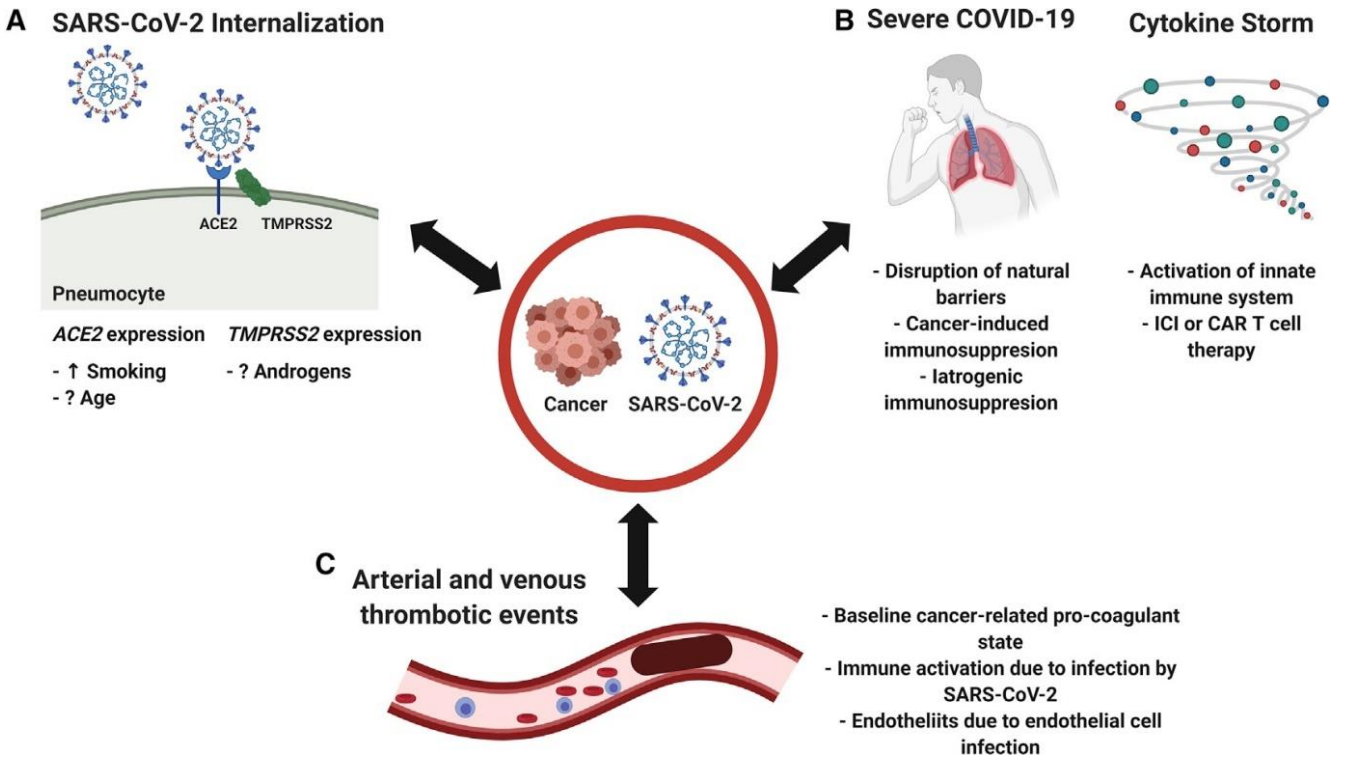

Figure 2. The Relationship between SARS-CoV-2 and Cancer Pathways [34]. (A) SARS-CoV-2 entry. (B) Immune system involvement. (C) Arterial and venous thrombosis.

manifestations. Understanding the biological mechanisms underlying the potential oncogenicity of SARS-CoV-2 is crucial for elucidating its effects on cancer development, progression, and treatment response.

3.1. Viral-Host Interactions

SARS-CoV-2 enters host cells by binding its spike protein to angiotensin-converting enzyme 2 (ACE2) receptors, which are abundantly present on the surface of respiratory epithelial cells. However, ACE2 expression is not restricted to the respiratory tract; it is also found in various extra-pulmonary tissues, including the gastrointestinal tract, kidneys, and vascular endothelium. The widespread distribution of ACE2 receptors suggests the potential for SARS- CoV-2 to infect diverse cell types, including those implicated [27]. Moreover, SARS-CoV-2 infection triggers dysregulation of host immune responses, leading to the release of pro-inflammatory cytokines and chemokines, a phenomenon known as cytokine storm. Chronic inflammation is central to the onset and advancement of cancer, as it facilitates genomic instability, cellular proliferation, angiogenesis, and metastasis. Therefore, the sustained inflammatory response elicited by SARS-CoV-2 infection may contribute to the oncogenic transformation of infected cells [28]. As a matter of fact, SARS-CoV-2 can cause direct impair to the tumor suppressor genes and gatekeepers p53 and pRb. [29] in addition to RB1 and E2F transcription factors [30]. Besides, SARS-CoV-2 leads to the progression of cancer by the process of autophagy for viral multiplication which can help to develop targeted therapy for the prevention of cancer development [31].

3.2. Immune Dysregulation

Patients with cancer are often immunocompromised due to the underlying disease, as well as cancer treatments such as chemotherapy, immunotherapy, and radiation therapy. Consequently, they may exhibit impaired immune surveillance and diminished antiviral defense mechanisms, rendering them more vulnerable to SARS-CoV-2 infection and associated complications. Furthermore, cancer-related immunosuppression may facilitate viral persistence, exacerbate inflammation, and promote viral oncogenesis through the evasion of immune surveillance mechanisms [32]. Additionally, SARS-CoV-2 has been shown to induce aberrant immune responses characterized by lymphopenia, dysfunctional T-cell activation, and exhaustion of natural killer (NK) cells. These immunological alterations may disrupt antitumor immune surveillance, compromise

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immune-mediated tumor control, and promote tumor immune evasion, thereby exacerbating oncogenesis in cancer patients [33].

3.3. Inflammatory Pathways

Chronic inflammation is a hallmark of cancer development and progression, with pro-inflammatory signaling pathways playing pivotal roles in oncogenic transformation, tumor proliferation, and metastasis. SARS-CoV-2 infection triggers a strong inflammatory response marked by increased levels of cytokines such as interleukin-6 (IL-6), interleukin-1 beta (IL-1β), and tumor necrosis factor-alpha (TNF-α). These cytokines promote tumor growth, angiogenesis, and metastasis through activation of downstream signaling cascades, including the Janus kinase/signal transducer and activator of transcription (JAK/STAT), nuclear factor-kappa B (NF-κB), and mitogen-activated protein kinase (MAPK) pathways [23]. Furthermore, dysregulation of the renin-angiotensin system (RAS) following SARS-CoV-2 infection may contribute to oncogenic processes by promoting cellular proliferation, angiogenesis, and fibrosis. Angiotensin II, a key effector molecule of the RAS, has been implicated in tumorigenesis and tumor progression through its pro-inflammatory, pro-angiogenic, and pro-fibrotic effects [35].

4. CLINICAL IMPLICATIONS AND MANAGEMENT STRATEGIES FOR CANCER PATIENTS DURING THE COVID-19 PANDEMIC

The COVID-19 pandemic has introduced significant obstacles for cancer care delivery, necessitating the implementation of innovative strategies to ensure optimal patient outcomes while minimizing the risk of SARS-CoV-2 spread. Here, we discuss the clinical implications of COVID-19 for cancer patients and explore management strategies aimed at mitigating the impact of the pandemic on oncological care. The COVID-19 pandemic has disrupted every aspect of cancer care delivery, from screening and diagnosis to treatment and follow-up. Screening programs for various cancers, including breast, colorectal, and cervical cancer, have been suspended or modified, leading to delays in early detection and diagnosis. Consequently, a backlog of undiagnosed and untreated cancers has accumulated, posing significant challenges for healthcare systems worldwide [42].

Moreover, the adoption of infection control practices, such as physical distancing, personal protective equipment (PPE) utilization, and telemedicine, has transformed the landscape of cancer care delivery. While these measures are crucial for mitigating the risk of SARS-CoV-2 transmission, they have also introduced logistical challenges and operational inefficiencies, resulting in delays in treatment initiation, modifications in treatment regimens, and disruptions in supportive care services [43].

To overcome these challenges, healthcare providers have adopted a variety of strategies to optimize cancer care delivery while ensuring patient safety and well-being. Telemedicine has emerged as a valuable tool for remote patient monitoring, symptom management, and follow-up care, allowing healthcare providers to maintain continuity of care while minimizing in-person interactions [44]. Furthermore, risk stratification and prioritization algorithms have been developed to guide clinical decision-making regarding cancer treatment initiation, modification, or deferral. Patients with aggressive or rapidly progressing cancers may require expedited treatment, whereas those with indolent or localized diseases may benefit from delayed or conservative management strategies to minimize the risk of COVID-19 exposure [45].

Moreover, multidisciplinary tumor boards and virtual consultations have facilitated collaborative decision-making among oncologists, surgeons, radiation oncologists, and other specialists, ensuring comprehensive and coordinated care for cancer patients during the pandemic. These forums provide opportunities for case discussion, treatment planning, and resource allocation, enabling healthcare providers to optimize treatment outcomes while adhering to infection control protocols [13].

In light of the psychosocial impact of the COVID-19 pandemic on cancer patients and their families, supportive care interventions and psychosocial support services have become integral components of oncological care delivery. Psychosocial distress, anxiety, depression, and financial concerns are common among cancer patients, exacerbated by the uncertainty and isolation associated with the pandemic [26]. To address these challenges, healthcare providers have implemented virtual support groups, counseling services, and educational resources to enhance coping skills, resilience, and emotional well-being among cancer patients and their caregivers. Additionally, financial assistance programs, transportation services, and housing support initiatives have been established to alleviate the economic burden and logistical barriers faced by underserved populations [14].

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Table 1. Biological Mechanisms Underlying the Potential Oncogenicity of SARS-CoV-2.

S/N	Biological Mechanisms	Factors influencing the mechanism	Reference(s)
1	Viral-Host Interactions	Cellular Receptors (e.g. ACE2 receptor)	[27]
		Viral Attachment and Entry (e.g. VTA1, KLF5, and DAZAP2)	[36]
		Host Cell Factors such as V-ATPases, ESCRT, and N-glycosylation components	[37][36]
2	Immune Dysregulation	Dysfunctional T-cell activation	[33]
		Viral Persistence and Disease Severity	[38]
		Aging	[39]
3	Inflammatory Pathways	Inflammatory Signaling Pathways	[35][40]
		Cytokine Storm	[23][41]

5. FUTURE DIRECTIONS AND RESEARCH PRIORITIES

As the COVID-19 pandemic continues to unfold, it is imperative to identify key areas for future research and prioritize efforts to address the evolving challenges posed by the intersection of SARS-CoV-2 and cancer. Here, we outline potential future directions and research priorities to advance our understanding of the COVID-19 and cancer nexus and improve clinical outcomes for affected individuals. One crucial area of investigation is the enduring effects of COVID-19 on cancer survivors, including its effects on cancer recurrence, treatment-related morbidity, and quality of life. Prospective cohort studies and longitudinal surveillance programs are needed to assess the incidence and severity of post-COVID complications among cancer survivors and identify risk factors associated with adverse outcomes. Additionally, interdisciplinary research collaborations involving oncologists, infectious disease specialists, and rehabilitation professionals are essential to develop tailored survivorship care plans and optimize long-term health outcomes for this vulnerable population.

Understanding the molecular mechanisms underlying viral oncogenesis and its contribution to cancer progression is another critical research priority. Preclinical models and in vitro studies can elucidate the interplay between SARS-CoV-2 infection and oncogenic pathways, facilitating the development of targeted therapies and immunomodulatory interventions for virus-associated malignancies. Furthermore, epidemiological studies and population-based registries are needed to assess the incidence and clinical characteristics of COVID-19-related cancers and elucidate the role of viral infections in cancer initiation, promotion, and metastasis. The COVID-19 pandemic has exacerbated existing health disparities and inequities in cancer care access, delivery, and outcomes. Future research efforts should concentrate on identifying high-risk groups for adverse COVID-19 outcomes, including racial and ethnic minorities, socioeconomically disadvantaged individuals, and rural communities. Community-based participatory research and health equity initiatives can inform targeted interventions to address systemic barriers to care and promote equitable access to COVID-19 testing, vaccination, and treatment for underserved populations.

Incorporating principles of implementation science and health system resilience into pandemic preparedness and response efforts is essential to optimize cancer care delivery during public health emergencies. Multidisciplinary research consortia and collaborative networks can facilitate knowledge translation, dissemination of best practices, and implementation of evidence-based interventions to enhance healthcare system capacity, surge capacity planning, and resource allocation strategies. Additionally, real-time data analytics and health informatics tools can inform decision-making, improve situational awareness, and monitor health outcomes in real time, enabling agile responses to emerge challenges and evolving threats.

Psychosocial and behavioral interventions play a crucial role in mitigating the psychosocial impact of the COVID-19 pandemic on cancer patients and their caregivers. Future research should aim to develop and assess telehealth-based psychoeducational programs, cognitive-behavioral therapies, and mindfulness-based interventions to address anxiety, depression, distress, and adjustment difficulties in the context of COVID-19. Moreover, community-based support networks, peer mentoring programs, and virtual support groups can foster social connectedness, resilience, and adaptive coping strategies among individuals affected by

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cancer and COVID-19. Interdisciplinary collaboration and knowledge translation are essential for translating research findings into actionable policies, programs, and practices to improve cancer care delivery and reduce the effects of the COVID-19 pandemic on oncological outcomes. Stakeholder engagement, patient advocacy, and community outreach initiatives can facilitate bidirectional communication, foster trust, and promote shared decision-making among healthcare providers, policymakers, researchers, and patients. By harnessing the collective expertise and resources of diverse stakeholders, we can advance the science of COVID-19 and cancer and develop innovative solutions to address the multifaceted challenges posed by this worldwide health crisis.

5. CONCLUSION

The intersection of SARS-CoV-2 and cancer presents a multifaceted challenge with far-reaching implications for oncogenesis, cancer care delivery, and public health. Epidemiological studies have highlighted the increased susceptibility of cancer patients to SARS-CoV-2 infection and its effects on cancer diagnosis, prognosis, and mortality. Moreover, our understanding of the biological mechanisms underlying the potential oncogenicity of SARS-CoV-2 has advanced significantly, revealing intricate interactions between viral-host dynamics, immune dysregulation, and inflammatory pathways implicated in cancer progression. These findings emphasize the importance of ongoing research to clarify the molecular mechanisms connecting viral infection to cancer and to identify potential therapeutic targets for intervention.

Clinical implications arising from the COVID-19 pandemic have prompted the development of innovative management strategies aimed at mitigating the impact of the pandemic on cancer care delivery. Telemedicine, risk stratification algorithms, and supportive care interventions have emerged as essential tools for optimizing patient outcomes while adhering to infection control protocols and resource constraints. Looking ahead, future research efforts should prioritize long-term surveillance of COVID-19 outcomes among cancer survivors, elucidation of viral oncogenesis mechanisms, addressing health disparities in cancer care, enhancing health system resilience, and fostering interdisciplinary collaboration. By leveraging the collective expertise and resources of the scientific community, we can navigate the challenges posed by the COVID-19 and cancer nexus and advance our understanding of the complex interplay between viral infection and oncological outcomes.

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