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Review Article

COVID-19, Long COVID, and Gastrointestinal Neoplasms: Exploring the Impact of Gut Microbiota and Oncogenic Interactions

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Abstract

Background: The impact of COVID-19 and long-term COVID-19 on gastrointestinal neoplasms remains underexplored. The current review investigates the potential link between these conditions and the role of gut microbiota in mediating oncogenic processes. Dysbiosis, characterized by alterations in gut microbial composition, may exacerbate inflammation and immune dysregulation, contributing to cancer development.

Methods: A comprehensive literature review was conducted using databases including PubMed, Scopus, Embase, SciELO, and Web of Science. Inclusion criteria encompassed studies published between 2020 and 2024 that explored the intersection of COVID-19, long-term COVID-19, and gastrointestinal cancers. The articles were critically appraised for quality and relevance, and data were synthesized to elucidate common mechanisms and outcomes.

Results: The review identifies several mechanisms by which gut microbiota may influence cancer risk in COVID-19 patients. Persistent inflammation, oxidative stress, and immune dysfunction observed in Long COVID were associated with dysbiosis. Specific microbial metabolites, such as secondary bile and short-chain fatty acids, were implicated in promoting tumorigenesis. Comparative analysis of studies suggests that SARS-CoV-2-induced dysbiosis may heighten susceptibility to gastrointestinal cancers, particularly in patients with prolonged post-infection symptoms.

Conclusion: The findings underscore the need for further research to clarify the role of gut microbiota in cancer development among COVID-19 patients. These mechanisms could inform preventative strategies and therapeutic interventions, particularly for those experiencing COVID. The review highlights gaps in current knowledge and advocates for longitudinal studies to assess the long-term effects of COVID-19 on gastrointestinal health.

Keywords: COVID-19; Long COVID; Gastrointestinal Neoplasms; Gut Microbiota; Inflammation; Oncogenesis

Introduction

COVID-19, caused by the SARS-CoV-2 virus, emerged as a global pandemic in late 2019, leading to an unprecedented public health crisis. The clinical presentation of COVID-19 varies widely, ranging from asymptomatic infections to severe respiratory illness, multi-organ failure, and death [1-3]. While most individuals recover within a few weeks of infection, a significant subset of patients experience persistent symptoms extending beyond the illness's acute phase. This condition, often referred to as "Long COVID" or "Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)," has become a focal point of ongoing medical research due to its chronic and often debilitating nature [4-6]. Long COVID is characterized by a broad spectrum of symptoms that persist for weeks or months after the initial SARS-CoV-2 infection has resolved. These symptoms can include, but are not limited to, fatigue, dyspnea, chest pain, cognitive dysfunction ("brain fog"), gastrointestinal disturbances, and musculoskeletal pain [7-8]. In contrast, "COVID-19" refers to the acute phase of infection, typically marked by symptoms such as fever, cough, shortness of breath, and other respiratory manifestations that generally resolve within a few weeks in most patients. The distinction between these two conditions lies primarily in their duration and symptomatology [9]. At the same time, COVID-19 represents the initial, often acute, phase of the viral infection. Long COVID-19 denotes a prolonged state where symptoms continue or develop well after the acute phase [10]. The pathophysiology of long-term COVID remains poorly understood. Still, it is believed to involve a complex interplay of immune dysregulation, persistent viral particles, and host factors such as age, sex, and pre-existing conditions. Emerging evidence suggests that the gut microbiota may play a crucial role in the persistence of symptoms in Long COVID patients [11-13]. The COVID-19 pandemic, instigated by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has precipitated an unparalleled global health crisis with multifaceted impacts on public health and clinical practices [14].

Initially recognized for its acute respiratory manifestations, the virus has since been implicated in a spectrum of prolonged health issues, collectively termed "Long COVID" or Post-Acute Sequelae of COVID-19 (PASC), and in the potential exacerbation or onset of various chronic diseases, including gastrointestinal (GI) cancers [4-7].

Long COVID is characterized by symptoms persisting for weeks or months after the acute phase of COVID-19 has resolved. These symptoms, which can affect multiple organ systems, significantly impair individuals' quality of life and functionality. Emerging research highlights the pivotal role of the gut microbiota in the pathogenesis of Long COVID [8-12].

The gut microbiome, a complex community of microorganisms residing in the gastrointestinal tract, is integral to maintaining homeostasis, regulating the immune system, and supporting metabolic processes [15-16]. Dysbiosis, or an imbalance in the gut microbial community, has been associated with both acute COVID-19 severity and the long-term sequelae seen in Long-term COVID2. It is hypothesized that alterations in the gut microbiota could contribute to a sustained inflammatory response, immune dysfunction, and metabolic disturbances, thereby exacerbating symptoms and prolonging recovery [8-10]. Given the prolonged course of Long COVID and its association with various systemic manifestations, including gastrointestinal symptoms, understanding the underlying mechanisms, particularly the role of the gut microbiota, is critical [14]. This distinction between the acute and long-term phases of COVID-19 is essential for developing targeted therapeutic strategies and guiding future research to mitigate the long-term impacts of SARS-CoV-2 infection [16,17]. The connection between gut microbiota and Long-term COVID is underscored by studies demonstrating that microbiota composition correlates with symptom severity and duration. This suggests gut dysbiosis may contribute to Long COVID's chronic inflammation and immune dysfunction [18-20]. Potential therapeutic interventions, such as probiotics, prebiotics, dietary modifications, and antibiotics, are being explored to restore gut microbiota balance and alleviate symptoms [21,22]. However, the complexity of the gut microbiome and its interactions with host physiology necessitates further research to elucidate the precise mechanisms through which gut dysbiosis influences Long COVID and to develop standardized therapeutic strategies [23-26].

The relationship between COVID-19 and the development or progression of gastrointestinal cancers is an area of active investigation. The SARS-CoV-2 virus, known to cause systemic inflammation and immune dysregulation, has been detected in tissue samples from the gastrointestinal tract, including the esophagus and stomach. This raises the possibility that the virus may directly contribute to oncogenesis in these tissues [27-30]. In addition, COVID-19's induction of a hyper inflammatory state, characterized by elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1beta (IL-1β), may create a pro-tumorigenic environment conducive to cancer development [31-33]. Chronic inflammation is a well-established risk factor for various cancers, including the digestive system. The persistent inflammatory response in COVID-19 patients, coagulation disorders, and oxidative stress may promote genetic mutations and epigenetic modifications that facilitate oncogenesis [34-36]. Furthermore, the immunosuppressive effects of COVID-19 can impair the body's ability to detect and eliminate emerging tumor cells, thereby accelerating cancer progression [37]. The interplay between Long COVID and gastrointestinal cancers underscores the complex and multifactorial nature of these conditions. Parallels have been drawn between long-term COVID-19 and chronic diseases such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), with gut microbiota alterations being a standard feature38. Understanding these parallels is crucial for developing comprehensive therapeutic approaches targeting gut dysbiosis and chronic inflammation [39].

In the context of gastrointestinal cancers, the pandemic has further complicated the landscape by disrupting routine healthcare services, leading to delays in cancer diagnosis and treatment. This disruption may result in more advanced disease stages at diagnosis, adversely affecting patient outcomes. The

potential for SARS-CoV-2 to exacerbate pre-existing conditions or contribute to new oncogenic pathways warrants extensive investigation [40]. Regarding the dual challenge of Long COVID and gastrointestinal cancers requires a multifaceted approach. For Long COVID, interventions that restore gut microbiota balance, such as probiotics, prebiotics, and dietary modifications, show promise [41]. However, robust clinical trials are needed to validate these strategies and determine their long-term efficacy and safety. For gastrointestinal cancers, early detection and timely treatment remain paramount. Integrating COVID-19 vaccination into cancer care protocols is safe and effective, providing additional protection for this vulnerable population [42-44]. Researchers should focus on longitudinal studies to track long-term gut microbiota changes in Long-term COVID patients and assess their impact on disease progression and response to interventions [45]. Similarly, large-scale epidemiological studies are needed to quantify the risk of gastrointestinal cancers in COVID-19 survivors and identify potential biomarkers for early detection [46].

COVID-19 pandemic has unveiled complex interconnections between viral infections, chronic diseases, and cancer development. Long COVID and gastrointestinal cancers represent significant public health challenges that require integrated research and clinical strategies47,48. Understanding the role of gut microbiota in Long-term COVID and the oncogenic potential of SARS-CoV-2 in the gastrointestinal tract is crucial for developing effective therapeutic interventions and improving patient outcomes [49]. This review aims to synthesize existing literature to elucidate the complex interplay between these conditions and propose future research and clinical practice directions.

Methods

The research strategy employed in this study was meticulously designed to encompass an exhaustive review of the literature across several distinguished databases known for their extensive collection of medical and scientific peer-reviewed publications. The selected databases for this comprehensive search included PubMed, Scopus, SciELO, Embase, and Web of Science, each renowned for their vast repository of scholarly articles. Additionally, Google Scholar was a supplementary resource for accessing gray literature, which often contains significant studies and reports unavailable in conventional academic journals. This approach ensured that the review incorporated a broad spectrum of evidence, including studies that may not have been captured in traditional academic databases. This research focused on exploring the relationship between COVID-19, long-term COVID-19, gastrointestinal neoplasms, and the potential role of gut microbiota in these processes. The intersection of these critical topics guided the formulation of search parameters. A carefully curated set of keywords was deployed to optimize the search, including terms such as "COVID-19," "Long COVID," "Gastrointestinal Neoplasms," "Gut Microbiota," "Inflammation," and "Oncogenesis." This strategic combination of keywords was instrumental in filtering the literature to include studies directly pertinent to the research objectives. The search was conducted without time restrictions, allowing the inclusion of the most recent and relevant studies. To ensure a broad yet relevant data collection, the inclusion criteria were designed to be comprehensive, welcoming a variety of study designs. Eligible studies included systematic reviews, cohort studies, case-control studies, cross-sectional analyses, case series, and scholarly reviews. This diversity in study types aimed to capture a wide range of evidence and perspectives regarding the impact of COVID-19 and long-term COVID-19 on gastrointestinal neoplasms and the role of gut microbiota in these processes. The inclusion criteria also mandated that studies be published in English and provide sufficient methodological detail to support qualitative synthesis. The literature review and selection process were executed with strict methodological rigor. Initially, pairs of reviewers independently evaluated the titles and abstracts of identified studies for relevance to the study's objectives. Full-text articles were then reviewed in detail to ensure conformity to the predefined inclusion criteria. Discrepancies between reviewers were resolved through consultation with a third independent reviewer to reach a consensus, ensuring the selection process was based on solid and unbiased judgment. This dual-review system, combined with a third reviewer in case of disagreement, enhanced the reliability of the study selection process. Data were extracted using a standardized extraction form, which included study characteristics such as author, year of publication, study type, sample size, population details, and outcomes related to the gut microbiota and gastrointestinal neoplasms in the context of COVID-19 and long-term COVID-19. The primary focus was identifying mechanisms by which gut microbiota may influence chronic inflammation and oncogenesis in post-COVID-19 patients. Extracted data were then synthesized qualitatively, as the heterogeneity in study designs, populations, and outcomes precluded a quantitative meta-analysis. The synthesis provided a comprehensive overview of the existing literature and identified key findings and gaps in knowledge related to the interplay between gut microbiota, COVID-19, and cancer development. This detailed and systematic approach to research methodology underpins the reliability and validity of the findings presented in this review. The conclusions drawn from this study are grounded in a critically evaluated body of scientific evidence related to the role of gut microbiota in gastrointestinal neoplasms following COVID-19, ensuring that the study contributes meaningful insights to the existing literature on this crucial intersection of microbiology, oncology, and virology.

Results

The ongoing COVID-19 pandemic has catalyzed extensive research into its diverse health impacts, notably its relationship with gastrointestinal neoplasms. Clinical studies have documented the presence of SARS-CoV-2 in gastrointestinal tissues, including the esophagus and stomach, suggesting a direct viral involvement in these organs [50-52]. The virus's presence in these tissues, confirmed through biopsies, indicates potential oncogenic pathways activated by SARS-CoV-2. The hyperinflammatory state induced by COVID-19, characterized by elevated levels of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β, creates a pro-tumorigenic environment conducive to developing and progressing gastrointestinal cancers [53,54].

Chronic inflammation, a well-known risk factor for various cancers, is significantly exacerbated by SARS-CoV-2 infection. The persistent inflammatory response, systemic coagulation disorders, and oxidative stress promote genetic mutations and epigenetic modifications that facilitate oncogenesis [55,56]. In addition, the immunosuppressive effects of COVID-19 impair the body's ability to detect and eliminate emerging tumor cells, thereby accelerating cancer progression. This multifactorial impact underscores the need to understand how COVID-19 influences gastrointestinal carcinogenesis comprehensively [28-30].

Discussion

Long COVID, characterized by prolonged symptoms persisting for weeks or months post-acute infection, has further underscored the complex interactions between COVID-19 and chronic disease. Emerging evidence highlights the significant role of gut microbiota in the pathogenesis of Long COVID [57-59]. Dysbiosis, or an imbalance in the gut microbiome, is frequently observed in Long COVID patients. This dysbiosis is marked by reduced beneficial commensal bacteria and increased pathogenic and pro-inflammatory taxa [25]. Such microbial imbalances are thought to contribute to immune dysfunction and chronic inflammation, which are hallmarks of long-term COVID-19 [60-62]. Researches have demonstrated that the gut microbiota composition correlates with the severity and duration of Long COVID symptoms. This suggests that gut dysbiosis may be critical in chronic inflammation and immune dysregulation of these patients [63]. Potential therapeutic interventions, such as probiotics, prebiotics, dietary modifications, and antibiotics, are being explored to restore gut microbiota balance and alleviate symptoms64-66. However, the complexity of the gut microbiome and its interactions with host physiology necessitates further research to elucidate the precise mechanisms through which gut dysbiosis influences Long COVID and to develop standardized therapeutic strategies [67-69]. The intersection between long-term COVID and gastrointestinal neoplasms underscores these conditions' complex and multifactorial nature. Parallels have been drawn between long-term COVID-19 and chronic diseases such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), with gut microbiota alterations being a standard feature. Understanding these parallels is crucial for developing comprehensive therapeutic approaches targeting gut dysbiosis and chronic inflammation37-40. The impact of gut microbiota on the progression of gastrointestinal diseases, particularly in the context of COVID-19 and Long COVID, has gained considerable attention in recent research. Dysbiosis, or an imbalance in the microbial community, has been identified as a critical factor influencing the severity and persistence of Long-term COVID symptoms and potentially increasing the risk of gastrointestinal cancers14,16. Recent studies have highlighted mechanisms through which the gut microbiota contributes to carcinogenesis, particularly in the gastrointestinal tract. For example, microbiota-derived bile acids have been shown to influence intestinal immunity and inflammation, which are crucial in developing gastrointestinal cancer. Bile acids, particularly secondary bile acids metabolized by gut bacteria, modulate the host's immune response through receptors such as FXR and TGR5 [5,26]. These interactions can activate inflammatory pathways, such as NF-κB, contributing to a pro-tumorigenic environment. In long-term COVID-19, where persistent inflammation is a hallmark, such mechanisms may exacerbate the chronic inflammatory state, potentially increasing the risk of gastrointestinal neoplasms. Alterations in gut microbiota and bile acid metabolism could underlie the increased cancer susceptibility observed in patients with prolonged COVID-19 symptoms [1,2].

Furthermore, the interactions between gut microbiota and colorectal cancer involve several microbial species that produce genotoxins, such as colibactin and enterotoxigenic Bacteroides fragilis (ETBF), which cause DNA damage and promote inflammation. These mechanisms are critical in the tumorigenesis of the colorectal region. Given that COVID-19 and Long COVID can significantly alter gut microbiota composition, these changes might promote the proliferation of such oncogenic bacteria, thereby enhancing the risk of colorectal cancer. A deeper understanding of how gut microbial shifts in patients recovering from COVID-19 could predispose them to oncogenesis through these documented pathways is needed [3,17]. Alterations in the gut microbiota composition can also influence tumor progression, particularly in colorectal cancer. For instance, specific pathogens, such as Fusobacterium nucleatum, can promote tumor adhesion and invasion while modulating inflammatory cytokines to create a microenvironment conducive to tumor growth. In the context of Long COVID, prolonged infection may lead to persistent dysbiosis, fostering conditions that support tumor progression. Managing gut microbiota alterations in COVID-19 patients could mitigate the risks of colorectal cancer progression [4,25]. Gut microbial metabolites, such as short-chain fatty acids (SCFAs) and secondary bile acids, play significant roles in colorectal carcinogenesis. These metabolites can directly influence the inflammatory milieu and immune responses within the gut, contributing to tumor initiation and growth. Understanding how dysbiosis resulting from Long COVID might alter these metabolic pathways is crucial, as it could exacerbate the risk of cancer development. Thus, microbial metabolites are critical factors in the oncogenic process in COVID-19 patients [5,38].

The broader implications of gut microbiota in cancer development and therapy are also substantial. The microbiome can promote or inhibit cancer depending on the microbial composition and host interactions. Therapeutic interventions targeting gut microbiota, such as probiotics or fecal microbiota transplantation (FMT), could be particularly beneficial in COVID-19 patients exhibiting dysbiosis and at increased risk for gastrointestinal cancers. Modulating the gut microbiota could be a preventive strategy against cancer in high-risk populations, such as those with Long COVID-19 [16,42]. The pandemic has further complicated the landscape of gastrointestinal cancer management by disrupting routine healthcare services, leading to delays in cancer diagnosis and treatment10-12. This disruption has resulted in more advanced disease stages at diagnosis, adversely affecting patient outcomes. Moreover, the potential for SARS-CoV-2 to exacerbate pre-existing conditions or contribute to new oncogenic pathways warrants

extensive investigation [53,54]. Addressing the dual challenge of Long COVID and gastrointestinal cancers requires a multifaceted approach. Investigating long COVID interventions that restore gut microbiota balance, such as probiotics, prebiotics, and dietary modifications, show promise [36-38]. These studies collectively highlight multiple mechanisms by which the gut microbiota can contribute to the development and progression of gastrointestinal cancers in the context of COVID-19 and Long COVID. Fundamental mechanisms include the modulation of immune responses, production of carcinogenic metabolites, and direct DNA damage by microbial toxins. Inflammatory cytokines such as IL-6 and TNF-α, produced in response to microbial dysbiosis, are critical mediators of intestinal injury and oxidative stress, contributing to a pro-tumorigenic environment. This chronic inflammatory state, exacerbated by the persistence of SARS-CoV-2, could promote carcinogenesis at both the genetic and cellular levels. Robust clinical trials are needed to validate these strategies and determine their long-term efficacy and safety. Exploring gastrointestinal cancers, early detection, and timely treatment remain paramount. Integrating COVID-19 vaccination into cancer care protocols is safe and effective, providing additional protection for this vulnerable population [70-71]. Future research should focus on longitudinal studies to track long-term gut microbiota changes in Long-term COVID patients and assess their impact on disease progression and response to interventions41-43. Large-scale epidemiological studies are needed to quantify the risk of gastrointestinal cancers in COVID-19 survivors and identify potential biomarkers for early detection33. The precise mechanisms through which SARS-CoV-2 influences cancer development and progression will be crucial for developing targeted therapeutic interventions [62]. The immune system's role in these processes is essential. COVID-19 infection leads to a complex interplay of immune responses, which can either suppress or promote tumor growth9-12. For instance, the virus-induced hyperinflammatory state may lead to an environment conducive to tumorigenesis through chronic inflammation and immune evasion mechanisms. Conversely, the immune system's efforts to combat the virus may inadvertently target tumor cells, suggesting potential therapeutic avenues using immune modulation [58-60].

Another critical area of research is understanding the impact of lifestyle changes due to the pandemic on cancer risk and progression. The pandemic has led to increased stress, changes in diet, and reduced physical activity, all of which can influence cancer risk [6-8]. These factors can alter the gut microbiota and immune responses, further complicating the relationship between COVID-19, long-term COVID-19, and gastrointestinal neoplasms [34,57]. Despite significant progress, several gaps in knowledge need to be addressed. The long-term impact of SARS-CoV-2 on the gastrointestinal tract and its potential to initiate or accelerate oncogenic processes remains inadequately understood. More comprehensive studies are needed to establish causality between COVID-19, Long COVID, and gastrointestinal cancer development [25,42]. The role of specific bacterial taxa in the gut microbiota that might confer susceptibility or resilience to long-term COVID-19, and gastrointestinal neoplasms requires further investigation44,68. The variability in individual responses to gut microbiota-targeted therapies also poses a challenge, highlighting the need for personalized approaches in treatment [71]. This review, however, is limited by the heterogeneity of the studies included, which precludes a quantitative meta-analysis. Additionally, there is a scarcity of longitudinal studies that directly investigate the long-term effects of SARS-CoV-2 on gut microbiota and its role in cancer development. Future research should focus on elucidating these mechanisms through well-designed, prospective trials better to understand the full impact of COVID-19 on gastrointestinal health.

Conclusion

In conclusion, the COVID-19 pandemic has unveiled complex interconnections between viral infections, chronic diseases, and cancer development. Long COVID and gastrointestinal cancers represent significant public health challenges that require integrated research and clinical strategies.

Understanding the role of gut microbiota in Long-term COVID and the oncogenic potential of SARS-CoV-2 in the gastrointestinal tract is crucial for developing effective therapeutic interventions and improving patient outcomes. This review aims to synthesize existing literature to elucidate the complex interplay between these conditions and propose directions for future research and clinical practice. As our understanding of these conditions evolves, it will be essential to integrate multidisciplinary approaches that consider the multifactorial nature of these diseases and their interconnections, ultimately improving patient care and outcomes in the post-pandemic era.

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Conflict of interest

The authors declare that there is no conflict of interest.

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