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Comment on “Crosstalk between gut microbiota and COVID-19 impacts pancreatic cancer progression”

Yang J *et al.* COVID-19 affects pancreatic cancer progression

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has become a global burden, further exacerbating the occurrence of risk events in cancer patients. The high risk of death from pancreatic cancer makes it one of the most lethal malignancies. Recently, Zhang *et al* reported in the *World Journal of Gastrointestinal Oncology* that COVID-19 influences pancreatic cancer progression *via* the lung-gut-pancreatic axis, and they provided insights into the intrinsic crosstalk mechanisms in which the gut microbiota is involved, the characteristics and effects of inflammatory factors, and immunotherapeutic strategies for treating both diseases. Here, we review the latest cutting-edge researches in the field of the lung-gut-pancreatic axis and discuss future perspectives to address the severe survival challenges posed by the COVID-19 pandemic in patients with pancreatic cancer.

Key Words: COVID-19; Pancreatic cancer; Lung-gut-pancreatic axis; Gut microbiota; Inflammatory factors; Immunotherapeutic

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Core Tip: The coronavirus disease 2019 (COVID-19) pandemic has become a global burden, further exacerbating the occurrence of mortality risk events in patients with pancreatic cancer. The aim of this new article is to highlight the need for lung-gut-pancreatic axis-based studies with a focus on intra-axis microbiota crosstalk and potential mechanisms of association to address the severe survival challenges posed by the COVID-19 pandemic in patients with pancreatic cancer.

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TO THE EDITOR

The coronavirus disease 2019 (COVID-19) pandemic has become a global burden, further exacerbating the occurrence of risk events in patients with cancer^[1,2]. Contracting COVID-19 significantly increases the risk of morbidity, mortality, and ICU admission in patients with cancer^[3]. Additionally, cancer patients have a 60% increased risk of contracting COVID-19 compared with patients without cancer^[4]. Owing to the worsening disease and poorer prognosis resulting from COVID-19 in patients with cancer, this patient group is considered a high-risk vulnerable population^[5]. The high risk of death from pancreatic cancer makes it one of the most lethal malignancies^[6], and the COVID-19 pandemic not only poses a survival challenge for patients with pancreatic cancer but also seriously threatens the execution of pancreatic cancer research^[7]. We are very interested in the review by Zhang *et al*^[8] published in the August 2022 issue of the *World Journal of Gastrointestinal Oncology*. We consider it to be a good quality review because the authors included in their article many articles from international high-quality journals, such as *Lancet*, *JAMA*, *Nature*, and *Cell*, and the article conclusions accurately and clearly summarize the findings of the included literature. From the 98 literature reviews included by the authors, they identified a key connector between COVID-19 and pancreatic cancer; that is, the gut microbiota regulates the host systemic immune response. The question highlighted by Zhang *et al*^[8] is how COVID-19 affects pancreatic cancer progression, *i.e.*, *via* the lung-gut-pancreatic axis, and the authors explained the physiological basis, relevance, and potential

biological mechanisms of targeting this axis. The novelty of the article is that, the authors highlight therapeutic perspectives in response to COVID-19 and pancreatic cancer based on the intrinsically linked mechanisms of the lung-gut-pancreatic axis, including dietary interventions to stabilize the endostasis of the intestinal flora, the therapeutic efficacy of pharmacological interventions, and strategies to manage inflammatory storms. We thank Zhang *et al*^[8] for their review, which has been instrumental in exploring pancreatic cancer treatment options and the development of risk event prevention programs in the context of the severe challenges of the COVID-19 pandemic.

¹ Regional citrate anticoagulation (RCA) is an artificial intelligence technology-based open multidisciplinary citation analysis database. We searched the RCA database for articles in cutting-edge fields in the last 2 years using the search terms “COVID-19”, “pancreatic cancer”, and “gut microbiota”. In addition to highlighting that the gut microbiota regulates immune and inflammatory responses to influence disease severity in COVID-19 and pancreatic cancer^[9,10], recent studies have revealed a complex intrinsic association between the three. Current studies indicate that the microbiota alters the malignant phenotype and prognosis of pancreatic cancer in ways that include stimulating persistent inflammation, altering the tumor microenvironment, modulating the anti-tumor immune system, and affecting cellular metabolism^[11]. The emerging link between the gut microbiota and pancreatic cancer has recently highlighted the concept of local (direct pancreatic effects) and remote (non-pancreatic) effects of bacteria on organ physiology, which offers potential therapeutic options for pancreatic cancer^[12]. However, research on the microbiota influencing pancreatic cancer progression has focused mainly on bacteria, and studies involving intestinal fungi and viruses are just starting to be published^[12]. Future work on how these gut microbes are intrinsically linked and on the exact mechanisms by which they influence pancreatic cancer progression is needed. The latest cutting-edge research has bridged the gap between COVID-19 and the gut microbiota, discovering mechanisms that link the gut microbiota to the ³ expression of the viral entry receptor angiotensin-converting enzyme 2 (ACE2)^[13],

the inflammatory response^[14], the immune homeostasis^[15], the microbiota metabolism^[16], and the “gut-lung axis”^[17]. In COVID-19, the main factor associated with disease severity is the involvement of a cytokine storm in the immune response, i.e., tissue damage and systemic inflammation^[13]. The gut microbiota may influence the severity of COVID-19 by regulating the host immune response^[18]. However, it is unclear whether the reported gut microbial changes are directly responsible for the inflammatory storm in patients with COVID-19 or if they represent the result of severe disease^[19], and future studies investigating these possibilities are pending. Zhang *et al*^[8] reported that the inflammation-induced immune response is an intrinsic mechanism through which the lung-gut-pancreatic axis produces crosstalk between COVID-19 and pancreatic cancer. On the basis of this mechanism, the authors proposed some strategies on how to manage COVID-19 and pancreatic cancer, including the regulation of microbiota homeostasis to improve patient immunity and the application of anti-inflammatory drugs to reduce the amount of inflammatory damage^[8]. However, the survival outcomes of applying these strategies for treating COVID-19 and pancreatic cancer co-morbidity and the effectiveness of such strategies during radiotherapy are not yet known. Future studies could focus on these issues. In conclusion, COVID-19 impacts pancreatic cancer progression based on lung-gut-pancreatic axis, nevertheless, more studies investigating the potential mechanisms of the crosstalk between COVID-19, pancreatic cancer and gut microbiota are needed in patients with COVID-19 and pancreatic cancer co-morbidity to achieve a better management. Focusing on the lung-gut-pancreatic axis is expected to move us into a new paradigm of treatment for COVID-19 in patients with pancreatic cancer.

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