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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

Jian Yang, Ying Liu, Shi Liu

**Jian Yang, Shi Liu,** Central Laboratory, the Third Affiliated Hospital, Qiqihar Medical University, Qiqihar 161000, Heilongjiang Province, China

**Ying Liu,** Department of Medical Oncology, the Third Affiliated Hospital, Qiqihar Medical University, Qiqihar 161000, Heilongjiang Province, China

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**Corresponding author: Shi Liu, PhD, Chief Physician,** Central Laboratory, the Third Affiliated Hospital, Qiqihar Medical University, No. 27 Taishun Street, Tiefeng District, Qiqihar 161000, Heilongjiang Province, China. shiliu2199@163.com

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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, it was reported in the *World Journal of Gastrointestinal Oncology* that COVID-19 influences pancreatic cancer progression *via* the lung–gut–pancreatic axis, and the authors 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.

**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.

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 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.

**REFERENCES**

1 **Kuderer NM**, Choueiri TK, Shah DP, Shyr Y, Rubinstein SM, Rivera DR, Shete S, Hsu CY, Desai A, de Lima Lopes G Jr, Grivas P, Painter CA, Peters S, Thompson MA, Bakouny Z, Batist G, Bekaii-Saab T, Bilen MA, Bouganim N, Larroya MB, Castellano D, Del Prete SA, Doroshow DB, Egan PC, Elkrief A, Farmakiotis D, Flora D, Galsky MD, Glover MJ, Griffiths EA, Gulati AP, Gupta S, Hafez N, Halfdanarson TR, Hawley JE, Hsu E, Kasi A, Khaki AR, Lemmon CA, Lewis C, Logan B, Masters T, McKay RR, Mesa RA, Morgans AK, Mulcahy MF, Panagiotou OA, Peddi P, Pennell NA, Reynolds K, Rosen LR, Rosovsky R, Salazar M, Schmidt A, Shah SA, Shaya JA, Steinharter J, Stockerl-Goldstein KE, Subbiah S, Vinh DC, Wehbe FH, Weissmann LB, Wu JT, Wulff-Burchfield E, Xie Z, Yeh A, Yu PP, Zhou AY, Zubiri L, Mishra S, Lyman GH, Rini BI, Warner JL; COVID-19 and Cancer Consortium. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet* 2020; **395**: 1907-1918 [PMID: 32473681 DOI: 10.1016/S0140-6736(20)31187-9]

2 **Lee LY**, Cazier JB, Angelis V, Arnold R, Bisht V, Campton NA, Chackathayil J, Cheng VW, Curley HM, Fittall MW, Freeman-Mills L, Gennatas S, Goel A, Hartley S, Hughes DJ, Kerr D, Lee AJ, Lee RJ, McGrath SE, Middleton CP, Murugaesu N, Newsom-Davis T, Okines AF, Olsson-Brown AC, Palles C, Pan Y, Pettengell R, Powles T, Protheroe EA, Purshouse K, Sharma-Oates A, Sivakumar S, Smith AJ, Starkey T, Turnbull CD, Várnai C, Yousaf N; UK Coronavirus Monitoring Project Team, Kerr R, Middleton G. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. *Lancet* 2020; **395**: 1919-1926 [PMID: 32473682 DOI: 10.1016/S0140-6736(20)31173-9]

3 **Arayici ME,** Kipcak N, Kayacik U, Kelbat C, Keskin D, Kilicarslan ME, Kilinc AV, Kirgoz S, Kirilmaz A, Kizilkaya MA, Kizmaz IG, Kocak EB, Kochan E, Kocpinar B, Kordon F, Kurt B, Ellidokuz H. Effects of SARS-CoV-2 infections in patients with cancer on mortality, ICU admission and incidence: a systematic review with meta-analysis involving 709,908 participants and 31,732 cancer patients. *J Cancer Res Clin Oncol* 2022; 1-14 [PMID: 35831763 DOI: 10.1007/s00432-022-04191-y]

4 **Lee KA**, Ma W, Sikavi DR, Drew DA, Nguyen LH, Bowyer RCE, Cardoso MJ, Fall T, Freidin MB, Gomez M, Graham M, Guo CG, Joshi AD, Kwon S, Lo CH, Lochlainn MN, Menni C, Murray B, Mehta R, Song M, Sudre CH, Bataille V, Varsavsky T, Visconti A, Franks PW, Wolf J, Steves CJ, Ourselin S, Spector TD, Chan AT; COPE consortium. Cancer and Risk of COVID-19 Through a General Community Survey. *Oncologist* 2021; **26**: e182-e185 [PMID: 32845538 DOI: 10.1634/theoncologist.2020-0572]

5 **Zhang L**, Zhu F, Xie L, Wang C, Wang J, Chen R, Jia P, Guan HQ, Peng L, Chen Y, Peng P, Zhang P, Chu Q, Shen Q, Wang Y, Xu SY, Zhao JP, Zhou M. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. *Ann Oncol* 2020; **31**: 894-901 [PMID: 32224151 DOI: 10.1016/j.annonc.2020.03.296]

6 **Park W**, Chawla A, O'Reilly EM. Pancreatic Cancer: A Review. *JAMA* 2021; **326**: 851-862 [PMID: 34547082 DOI: 10.1001/jama.2021.13027]

7 **Casolino R**, Biankin AV; PanCaCovid-19 Study Group. Impact of COVID-19 on Pancreatic Cancer Research and the Path Forward. *Gastroenterology* 2021; **161**: 1758-1763 [PMID: 34389342 DOI: 10.1053/j.gastro.2021.06.080]

8 **Zhang CY**, Liu S, Yang M. Crosstalk between gut microbiota and COVID-19 impacts pancreatic cancer progression. *World J Gastrointest Oncol* 2022; **14**: 1456-1468 [PMID: 36160747 DOI: 10.4251/wjgo.v14.i8.1456]

9 **Donlan AN**, Sutherland TE, Marie C, Preissner S, Bradley BT, Carpenter RM, Sturek JM, Ma JZ, Moreau GB, Donowitz JR, Buck GA, Serrano MG, Burgess SL, Abhyankar MM, Mura C, Bourne PE, Preissner R, Young MK, Lyons GR, Loomba JJ, Ratcliffe SJ, Poulter MD, Mathers AJ, Day AJ, Mann BJ, Allen JE, Petri WA Jr. IL-13 is a driver of COVID-19 severity. *JCI Insight* 2021; **6** [PMID: 34185704 DOI: 10.1172/jci.insight.150107]

10 **Moslim MA**, Hall MJ, Meyer JE, Reddy SS. Pancreatic cancer in the era of COVID-19 pandemic: Which one is the lesser of two evils? *World J Clin Oncol* 2021; **12**: 54-60 [PMID: 33680873 DOI: 10.5306/wjco.v12.i2.54]

11 **Chen Z**, Zhang S, Dong S, Xu H, Zhou W. Association of the Microbiota and Pancreatic Cancer: Opportunities and Limitations. *Front Immunol* 2022; **13**: 844401 [PMID: 35309293 DOI: 10.3389/fimmu.2022.844401]

12 **Thomas RM**, Jobin C. Microbiota in pancreatic health and disease: the next frontier in microbiome research. *Nat Rev Gastroenterol Hepatol* 2020; **17**: 53-64 [PMID: 31811279 DOI: 10.1038/s41575-019-0242-7]

13 **Matheson NJ**, Lehner PJ. How does SARS-CoV-2 cause COVID-19? *Science* 2020; **369**: 510-511 [PMID: 32732413 DOI: 10.1126/science.abc6156]

14 **Del Valle DM**, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B, Lavin Y, Swartz TH, Madduri D, Stock A, Marron TU, Xie H, Patel M, Tuballes K, Van Oekelen O, Rahman A, Kovatch P, Aberg JA, Schadt E, Jagannath S, Mazumdar M, Charney AW, Firpo-Betancourt A, Mendu DR, Jhang J, Reich D, Sigel K, Cordon-Cardo C, Feldmann M, Parekh S, Merad M, Gnjatic S. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med* 2020; **26**: 1636-1643 [PMID: 32839624 DOI: 10.1038/s41591-020-1051-9]

15 **Sun Z**, Song ZG, Liu C, Tan S, Lin S, Zhu J, Dai FH, Gao J, She JL, Mei Z, Lou T, Zheng JJ, Liu Y, He J, Zheng Y, Ding C, Qian F, Zheng Y, Chen YM. Gut microbiome alterations and gut barrier dysfunction are associated with host immune homeostasis in COVID-19 patients. *BMC Med* 2022; **20**: 24 [PMID: 35045853 DOI: 10.1186/s12916-021-02212-0]

16 **Zhang F**, Wan Y, Zuo T, Yeoh YK, Liu Q, Zhang L, Zhan H, Lu W, Xu W, Lui GCY, Li AYL, Cheung CP, Wong CK, Chan PKS, Chan FKL, Ng SC. Prolonged Impairment of Short-Chain Fatty Acid and L-Isoleucine Biosynthesis in Gut Microbiome in Patients With COVID-19. *Gastroenterology* 2022; **162**: 548-561.e4 [PMID: 34687739 DOI: 10.1053/j.gastro.2021.10.013]

17 **Zhang D**, Li S, Wang N, Tan HY, Zhang Z, Feng Y. The Cross-Talk Between Gut Microbiota and Lungs in Common Lung Diseases. *Front Microbiol* 2020; **11**: 301 [PMID: 32158441 DOI: 10.3389/fmicb.2020.00301]

18 **Yeoh YK**, Zuo T, Lui GC, Zhang F, Liu Q, Li AY, Chung AC, Cheung CP, Tso EY, Fung KS, Chan V, Ling L, Joynt G, Hui DS, Chow KM, Ng SSS, Li TC, Ng RW, Yip TC, Wong GL, Chan FK, Wong CK, Chan PK, Ng SC. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. *Gut* 2021; **70**: 698-706 [PMID: 33431578 DOI: 10.1136/gutjnl-2020-323020]

19 **Zhang F**, Lau RI, Liu Q, Su Q, Chan FKL, Ng SC. Gut microbiota in COVID-19: key microbial changes, potential mechanisms and clinical applications. *Nat Rev Gastroenterol Hepatol* 2022; 1-15 [PMID: 36271144 DOI: 10.1038/s41575-022-00698-4]

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