

# World Journal of *Gastroenterology*

*World J Gastroenterol* 2022 May 28; 28(20): 2152-2250



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The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2021 edition of Journal Citation Report® cites the 2020 impact factor (IF) for WJG as 5.742; Journal Citation Indicator: 0.79; IF without journal self cites: 5.590; 5-year IF: 5.044; Ranking: 28 among 92 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG's CiteScore for 2020 is 6.9 and Scopus CiteScore rank 2020: Gastroenterology is 19/136.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: *Yu-Xi Chen*, Production Department Director: *Xu Guo*, Editorial Office Director: *Ze-Mao Gong*.

**NAME OF JOURNAL**

*World Journal of Gastroenterology*

**ISSN**

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

**LAUNCH DATE**

October 1, 1995

**FREQUENCY**

Weekly

**EDITORS-IN-CHIEF**

Andrzej S Tarnawski

**EDITORIAL BOARD MEMBERS**

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

**PUBLICATION DATE**

May 28, 2022

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## Future prospect of “Gut microbiome composition can predict the response to nivolumab in advanced hepatocellular carcinoma patients”

Yong-Bo Kang, Yue Cai

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): A  
Grade B (Very good): B  
Grade C (Good): 0  
Grade D (Fair): 0  
Grade E (Poor): 0

**P-Reviewer:** Gorrell MD, Australia; Yu L, Singapore

**Received:** December 10, 2021

**Peer-review started:** December 10, 2021

**First decision:** January 8, 2022

**Revised:** January 14, 2021

**Accepted:** April 24, 2022

**Article in press:** April 24, 2022

**Published online:** May 28, 2022



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### Abstract

Recently, we read the article “Gut microbiome composition can predict the response to nivolumab in advanced hepatocellular carcinoma patients” with interest, and it is preliminary suggested that gut microbiota is closely related to therapeutic effect of nivolumab. Based on the meaningful results of this article, several valuable research directions are proposed to enhance the therapeutic effect of immune checkpoint inhibitors on advanced hepatocellular carcinoma.

**Key Words:** Gut microbiome; Immunotherapy; Immune checkpoint inhibitor resistance; Probiotics; Faecal microbiota transplantation; Hepatocellular carcinoma; Prognosis

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**Core Tip:** We read the article “Gut microbiome composition can predict the response to nivolumab in advanced hepatocellular carcinoma patients” with interest, and it is preliminary suggested that the gut microbiota is closely related to therapeutic effect of nivolumab. Future research should pay attention to the relationship between the gut microbiota and therapeutic effect of immune checkpoint inhibitors (ICIs) on advanced hepatocellular carcinoma and the way of regulating the gut microbiota to improve the therapeutic effect of ICIs.

**Citation:** Kang YB, Cai Y. Future prospect of “Gut microbiome composition can predict the response to nivolumab in advanced hepatocellular carcinoma patients”. *World J Gastroenterol* 2022; 28(20): 2248-2250

**URL:** <https://www.wjgnet.com/1007-9327/full/v28/i20/2248.htm>

**DOI:** <https://dx.doi.org/10.3748/wjg.v28.i20.2248>

## TO THE EDITOR

We read with interest the article “Gut microbiome composition can predict the response to nivolumab in advanced hepatocellular carcinoma patients” [1], in which the authors analyzed and summarized the correlation between gut bacterial composition and the prognosis of nivolumab therapy in hepatocellular carcinoma (HCC) patients. The highlight of this article was that gut microbiota composition and diversity of responders differed significantly from those of non-responders following nivolumab therapy. Several intestinal bacterial species such as *Citrobacter freundii*, *Azospirillum species*, and *Enterococcus durans* were specific to the responders. Moreover, a higher *Prevotella/Bacteroides* ratio and the presence of *Akkermansia species* can serve as predictive markers of response. Altogether, the study not only demonstrated that the therapeutic effect of nivolumab has something to do with the composition of the gut microbiota in advanced HCC patients, but also provided some inspiration for future research direction.

In our opinion, it is of importance to underline that the relationship between the therapeutic effect of various immune checkpoint inhibitors (ICIs) such as pembrolizumab, nivolumab atezolizumab, durvalumab, and avelumab on HCC and the gut microbiota. At present, the response rates to ICIs are very low in advanced HCC. To be specific, the response rate to ICI monotherapy is merely 15%-23%, which is increased to approximately 30% after combination treatment [2]. How to improve the effectiveness of ICI treatment is essential and has been extensively investigated. While the human gut microbiota has been shown to be associated with clinical responses to ICIs in HCC [3], the available data in this field remain limited and the relevant scientific work is only in the initial stage. Thus, more research is required in the future. First, clinical studies with large sample sizes are needed to further clarify the relationship between the gut microbiota and the therapeutic effect of various ICIs. At the same time, which types of gut microbiota are suitable for which ICIs should also be figured out. Furthermore, construction based on the gut microbiota can function as a prognostic marker for the response to various ICI therapies. These results will provide clinicians with a valuable reference for rational use of ICIs and personalized precision therapy. Second, the mechanism by which the gut microbiota promotes the therapeutic effect of various ICIs needs to be further studied, with the focus on key pathways such as intestinal mucosal barrier function, bacterial metabolites, and microorganism-related molecular patterns, thus being conducive to discovering how to enhance the therapeutic effect of various ICIs by targeting the gut microbiota. Third, probiotics, prebiotics, synbiotics, and antibiotics may represent innovative, safe, and low-cost strategies for promoting the therapeutic effect of various ICIs [4]. In this respect, it is of necessity to determine which beneficial bacteria and harmful bacteria are bound up with the therapeutic effects of which ICIs. Meanwhile, it will also be significant to confirm how probiotics, prebiotics, synbiotics, and antibiotics alter the composition of the gut microbiota and how relevant it is to the therapeutic effect of various ICIs. In other words, these results will contribute to the identification of probiotics, prebiotics, synbiotics, and antibiotics that may increase the efficacy of ICIs when being used in combination. Last but not least, faecal microbiota transplantation (FMT) may be a direct and superior approach to enhancing the therapeutic effect of various ICIs through modulating the gut microbiota in human beings. Considering that, it is extremely valuable to explore the therapeutic method of FMT in combination with ICIs. Besides, the optimal gut microbiota composition for enhancing the therapeutic effect of various ICIs should be recognized. On this basis, it is of great importance to choose the right donors [5].

In summary, based on the meaningful research results of this article, it is expected that readers can pay attention to the relationship between the gut microbiota and therapeutic effect of ICIs on advanced HCC and the method of regulating the gut microbiota to improve the therapeutic effect of ICIs.

## FOOTNOTES

**Author contributions:** Kang YB and Cai Y wrote the letter and conceived the manuscript; Kang YB supervised the manuscript drafting and reviewed the literature data; and all authors contributed important intellectual content during manuscript drafting or revision.

**Conflict-of-interest statement:** There is no conflict to declare.

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**S-Editor:** Wang JJ

**L-Editor:** Wang TQ

**P-Editor:** Wang JJ

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