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Letter to the Editor

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# Was Concurrent Antibiotic Use during Immunotherapy Associated with Higher Mortality for Patients with Advanced Hepatocellular Carcinoma?

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Dear Editor,

We read with great interest the article by Dr. Cheung et al. [1]. This is a retrospective cohort study by using data from territory-wide electronic health-care database managed by the Hong Kong Hospital Authority. By the results of propensity score matching and multivariable regression analysis, they declared that concurrent use of antibiotics during immune checkpoint inhibitors therapy was associated with higher cancer-related and all-cause mortality in patients with advanced hepatocellular carcinoma (HCC). However, we would like to raise the following comments.

First, this study was conducted on the long-term prognosis after immunotherapy for patients with advanced HCC. However, surprisingly, there was the lack of some common baseline characteristics related to tumor burden, such as largest tumor size, tumor number, macrovascular invasion and/or distant metastasis, performance status, etc. Actually, these tumor-related variables are very important in this study, not only because these variables should be considered to be well matched by propensity score analysis between antibiotic users and nonusers but also because these potentially correlated variables should be taken into univariable and multivariable analyses associated with cancer-related and all-cause mortality. As we think, the possibility cannot be ruled out in this study that antibiotic users had a heavier tumor burden and a poorer tumor malignancy, resulting in a worse prognosis. These important confounding factors should be considered and at least emphasized as a limitation of this territory-based study.

Second, the authors did not mention whether so-called advanced HCC in this study was based on Barcelona clinic liver cancer (BCLC) staging system, as well as whether a small proportion of patients with unresectable but intermediate (BCLC stage B) HCC were also included in the whole cohort. We did not find the information on the specific numbers of these excluded patients in the figure of patient selection flow diagram (Fig. 1 of Cheung's study).

Third, in addition to the infection nature (anaerobic or aerobic) and duration of antibiotics, in our opinion, the site and severity of infectious diseases requiring antibiotic use for all analytic patients should be clarified in this study, considering its possible relationship with all-cause mortality, especially for noncancer-related mortality. Although the authors retrieved data of 76 antibiotic users in their own hospital and gave the indications of

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antibiotic use, it was far enough from a portrait of all 109 antibiotics users and would cause major biases in interpreting the results. Furthermore, we wondered whether higher mortality from those serious infectious diseases was also responsible for the higher all-cause mortality for antibiotic users, compared with antibiotic nonusers. Therefore, we suggest the authors supplement the time from antibiotic use to death, so that we can speculate if the cause of death for antibiotic users was related to their infectious diseases.

In conclusion, we believe that although based on a relatively large territory-based database, this study by Cheung et al. [1] has unreliable and imprecise conclusions due to the lack of some important outcome-related variables and the uncertainty of exclusion criteria. As we notice, the conclusion of Cheung's study is exactly opposite to that of Dr. Fessas's study published in the same journal [2]. We look forward to prospective studies with larger sample size and enough reliable variables in the future. In any case, we are very grateful to Dr. Cheung et al. [1] for their great efforts on this important issue.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.


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## Author Contributions

Jia-Yu Hu and Si-Yu Liu contributed equally to this work. Conception: Jia-Yu Hu, Chen Yuan, and Xiang-Min Tong; manuscript preparation: Jia-Yu Hu, Si-Yu Liu, and Chen Yuan; and critical revision: Xiang-Min Tong and Ying Wang. All the authors reviewed the paper and approved the final version.

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