

# Antibiotics Associated with Lower Survival in Hepatocellular Cancer Patients Receiving Immune Checkpoint Inhibitors Independent of Tumor Status

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We thank Hu et al. [1] for their comments on our recent manuscript entitled “Use of Antibiotics during Immune Checkpoint Inhibitor Treatment Is Associated with Lower Survival in Hepatocellular Carcinoma” [2]. Several issues were raised including adjustment of baseline factors that could affect prognosis of liver cancer, the Barcelona Clinic Liver Cancer (BCLC) staging system, and severity of infection that required antibiotic use.

In response, we were able to retrieve the details of 263 (66.6%) patients about the largest tumor size, number of liver tumor nodules, local macrovascular invasion, distant metastases, the Eastern Cooperative Oncology Group (ECOG) performance status, BCLC staging, and infection severity (defined as presence of shock or bacteremia) (Table 1). Among these patients, 245 (93.2%) had BCLC stage C or D. There was no statistically significant significance in these variables between antibiotic users and nonusers except for ECOG performance status  $\geq 3$  which was more common in antibiotic users (6 [8.7%] vs. 5 [2.6%];  $p = 0.040$ ). We have further adjusted for these factors in the propensity score regression model with the adjusted hazard ratio (aHR) of all-cause mortality of 1.58

(95% CI: 1.03–2.43;  $p = 0.035$ ) and cancer-related mortality of 1.57 (95% CI: 0.98–2.51;  $p = 0.063$ ). The borderline statistical significance of latter is likely due to underpower.

Concerning the site of infection, it was already presented in eTable 3 of the original article. Out of the 76 antibiotic users from our center, the most common indication for antibiotic use was a fever of unknown cause or empirical use ( $n = 35$ ), followed by pneumonia ( $n = 7$ ), gastrointestinal bleeding ( $n = 5$ ), and post-TACE fever ( $n = 5$ ).

The median time from receiving the first ICI to cancer-related and all-cause mortality should be 3.1 months (IQR: 1.6–6.7) and 3.2 months (IQR: 1.7–8.2), respectively, in which antibiotic use was defined as any use of antibiotics within 30 days before or after the receipt of first ICI. This precludes the possibility of reverse causality, in which severe infection preceding death mandates the use of antibiotics. This has been already included in the Discussion section of the original article.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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## Author Contributions

Dr. Ka Shing Cheung was involved with study concept and design, literature search, analysis and interpretation of data, drafting of manuscript, and approval of the final version of the manuscript. Dr. Lok Ka Lam was involved in data retrieval. Professor Wai K. Leung was involved with the study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, study supervision, and approval of the final version of the manuscript.

## References

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- 2 Cheung KS, Lam LK, Seto WK, Leung WK. Use of antibiotics during Immune Checkpoint inhibitor treatment is associated with lower survival in hepatocellular carcinoma. *Liver Cancer*. 2021;10(6):606–14.