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Letter to the Editor

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Impact of Antibiotics Use on Cancer-Related and All-Cause Mortality among Patients Receiving Immunotherapy for Advanced Hepatocellular Carcinoma

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Dear Editor,

We read with great interest the recent article by Dr. Cheung et al. [1]. By analyzing the data from the Clinical Data Analysis and Reporting System (CDARS) of Hong Kong, the authors evaluated the effect of antibiotic use on long-term prognosis for patients receiving immune checkpoint inhibitors (ICIs) therapy for advanced hepatocellular carcinoma (HCC). Using three statistical methods, i.e., propensity-score matching, propensity-score-regression adjustment, and multivariable Cox-regression analyses, this retrospective observational study demonstrated that concurrent antibiotic use during ICIs therapy was independently associated with higher cancer-related and all-cause mortality rates among patients with advanced HCC (all adjusted hazard ratios >1.5 with all $p < 0.05$). Although inspiring, we have the following comments.

As Cheung et al. [1] have pointed out in the Methods section, the primary and secondary outcomes of this study were cancer-related and all-cause mortality, respectively. Given that the Cox regression model was used in their multivariable analyses, it can be inferred here that these two outcomes are time-dependent variables, which can be equally regarded as cancer-related and all-caused survival [2]. However, it is puzzling why the authors did not mention the start time for these survival analyses. Was it the date of diagnosis of advanced HCC or the date of starting ICIs therapy? Moreover, why the authors did not exhibit the details of survival time, such as 1- and 2-year survival rates (i.e., cumulative time-to-mortality rates)? In our opinion, this important information could allow readers to learn more about the overall efficacy of ICIs therapy for the entire cohort and the two comparison cohorts. Considering that the figure form can make the results easier to understand than the table form, we suggest the authors preferably use the Kaplan-Meier curve with the log-rank test to intuitively show the cumulative survival (i.e., mortality) difference between antibiotic users and nonusers in their study.

As we think, one strength of this study by Cheung et al. [1] is the use of a territory-based dataset, which allows for a large sample size with the conclusions more suitable for real-world generalization. However, as for database research, such as using Surveillance, Epidemiology, and

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End Results (SEER) database [3] or National Cancer Database (NCDB) [4] of the USA, there are some inherent limitations, such as the always existing lack of potentially important variables related to study outcomes, inaccurate or difficult-to-judgment definition of variables or study outcomes, insufficient follow-up records, etc. In this study, according to the causes of death, Cheung et al. [1] divided the study outcome, all-cause mortality, into cancer-related and noncancer-related mortality. However, they did not give a specific definition of what is cancer-related or noncancer-related death. For example, for a cirrhotic patient receiving ICIs therapy for advanced HCC whose death was recorded as a result of upper gastrointestinal bleeding, how did the authors determine whether the death was due to side effect of ICIs therapy or decompensated liver cirrhosis? Was it a cancer-related or noncancer-related mortality? To our knowledge, even in those well-known nation-based databases including SEER and NCDB, relatively accurate causes of death are rarely recorded [3–5]. Therefore, given the importance of causes of death in the study by Cheung et al. [1], we wonder to know whether the details of causes of death could be easily accessed by the CDARS of Hong Kong. In conclusion, clarification regarding abovementioned omissions would greatly reinforce the validity and credibility for the conclusion of this study by Dr. Cheung et al. [1].

Conflict of Interest Statement

All authors have declared no conflict of interest.

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Author Contributions

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