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The double-edged sword: impact of antibiotic use on immunotherapy efficacy in advanced hepatocellular carcinoma

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Abstract

Objective This retrospective study aims to evaluate the impact of antibiotics (ATBs) use on the efficacy of immunotherapy in patients with advanced hepatocellular carcinoma (HCC), providing insights into the prudent use of ATBs in patients undergoing immunotherapy.

Methods We retrospectively collected data from patients with advanced HCC treated with immune checkpoint inhibitors (ICIs) at our institution between January 1, 2021, and December 30, 2023. Patients were divided into two groups based on ATBs use: an ATB group and a non-ATB group. Clinical baseline characteristics were analyzed, and survival curves were plotted using the Kaplan-Meier model. A Cox proportional hazards model was employed to analyze influencing factors.

Results Among the 102 advanced HCC patients receiving ICIs treatment, 29 were in the ATB group, and 73 were in the non-ATB group. The progression-free survival (PFS) ($P=0.034$) and overall survival (OS) ($P=0.021$) were significantly shorter in the ATB group compared to the non-ATB group. The difference in PFS between the two groups was associated with ATBs use and patients' AFP levels, while ATBs use was identified as an independent risk factor for the difference in OS between the groups.

Conclusion ATB use in the context of immunotherapy for advanced HCC is associated with reduced PFS and OS. Caution is warranted in the administration of ATBs to patients undergoing immunotherapy.

Keywords Hepatocellular carcinoma, Immune checkpoint inhibitor, Antibiotics, Survival analysis

Primary liver cancer is one of the most common malignant tumors of the digestive system worldwide, ranking sixth in incidence and fourth in mortality globally. According to estimates from the World Health Organization, approximately one million people will die from primary liver cancer by 2030 [1]. Hepatocellular carcinoma (HCC) accounts for about 85% of primary liver cancers [2]. The etiology of HCC is closely associated with chronic hepatitis caused by hepatitis B, hepatitis C, alcohol abuse, and metabolic syndrome [3]. Early-stage HCC often lacks obvious clinical symptoms, leading to diagnoses frequently occurring at advanced stages. This late diagnosis contributes to its aggressive nature, high recurrence rate, poor treatment outcomes, and unfavorable prognosis [4]. Currently, treatment options for HCC primarily include surgery, transarterial chemoembolization, and radiotherapy and chemotherapy. However, effective treatment strategies for advanced HCC remain limited.

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In recent years, the exploration and research into novel therapies for malignant tumors have brought increasing attention to immune checkpoint inhibitors (ICIs). ICIs exert antitumor effects by inhibiting the interaction between T lymphocyte receptors and their homologous ligands on tumor cells, thereby unleashing T lymphocyte-mediated immune responses [5]. In 2017, the U.S. FDA approved nivolumab for the second-line treatment of HCC, marking the beginning of a new era in HCC immunotherapy. In the CheckMate-040 study, 262 patients with advanced HCC were treated with nivolumab, resulting in an objective response rate (ORR) of 15–20% and a disease control rate (DCR) of 58–64% [6]. *Camrelizumab*, a humanized IgG4 monoclonal antibody developed in China, was approved for the second-line treatment of HCC in 2020. In a phase II clinical trial of camrelizumab, 220 patients received the drug as a second-line treatment, achieving an ORR of 14.7%, with a 6-month overall survival (OS) rate of 74.4% and a median OS of 13.8 months [7]. The rapid development of immunotherapy has opened a new chapter in the treatment of HCC, representing a promising direction for future therapies.

Cancer patients often experience immunological dysfunction, which not only drives tumor development and progression but also contributes to complications in multiple organs [8]. Additionally, the need for repeated hospitalizations for antitumor treatments makes cancer patients more susceptible to pathogenic microorganisms, resulting in severe infections. Studies have shown that bloodstream infections are a significant cause of death in neutropenic cancer patients [9]. Therefore, the rational use of antibiotics (ATBs) is critical when managing infections in cancer patients. However, two articles published in Science have raised concerns about the concomitant use of ATBs in cancer patients undergoing immunotherapy. These studies were the first to indicate that the gut microbiota may influence the antitumor efficacy of CTLA-4 and PD-L1 inhibitors [10, 11]. Mechanistic studies have demonstrated that the gut microbiota may influence the expression of T cells, such as Tregs and CD8 + T cells, and regulate the differentiation of monocytes into immunogenic dendritic cells [12]. In patients with advanced hepatobiliary carcinoma receiving PD-1 therapy, Lachnospiraceae bacterium-GAM79 and Alistipes sp. Marseille-P5997 were significantly enriched in the cohort benefiting from immunotherapy, whereas Veillonellaceae exhibited a higher abundance in the non-responding group [13]. Similarly, in patients with non-small cell lung cancer undergoing immunotherapy, gut microbiota diversity was found to be closely associated with PFS. Specifically, Alistipes shahii, Alistipes finegoldii, and Barnesiella visceriola were correlated with prolonged PFS (> 6 months), whereas Streptococcus salivarius, Streptococcus vestibularis, and Bifidobacterium breve were associated with shorter PFS (≤ 6 months) [14]. These findings underscore the critical role of gut microbiota in modulating systemic immune responses and shaping the efficacy of ICIs. In clinical observations, research by Tinsley et al. on 291 patients with advanced cancers treated with ICIs identified ATB use as an independent risk factor for reduced PFS and OS [15]. In a retrospective analysis by Derosa et al., involving 175 patients with advanced renal cell carcinoma, urothelial carcinoma, and non-small cell lung cancer treated with ICIs, those who received ATBs had significantly shorter median PFS and OS compared to those who did not [16]. These findings suggest that ATB use may impact the efficacy of ICIs.

The liver has a unique immune microenvironment, making it particularly responsive to immunotherapy. This suggests significant potential for immunotherapy in patients with advanced HCC [17]. However, studies specifically examining the impact of ATBs on the efficacy of immunotherapy in HCC are limited. Therefore, this study retrospectively analyzes real-world data from HCC patients in our hospital to explore the effect of ATB use on the outcomes of immunotherapy in advanced HCC, aiming to provide insights for the rational use of ATBs in cancer patients and to promote optimal clinical practices.

Materials and methods

General information

This retrospective study included 102 patients with advanced HCC who received ICIs at our hospital between January 1, 2021, and December 30, 2023. Relevant clinical data were collected from the electronic medical records system, including age, gender, treatment strategies, metastatic status, Eastern Cooperative Oncology Group (ECOG) performance status, alpha-fetoprotein (AFP) levels, and ATB usage. The inclusion criteria were as follows: (i) clinically confirmed diagnosis of HCC; (ii) age ≥ 18 years; (iii) China Liver Cancer (CNLC) staging of III-IV; (iv) ECOG performance status score ≥ 2; and (v) treatment with ICIs. Exclusion criteria included: (i) presence of other malignancies; (ii) loss to follow-up or incomplete clinical data; and (iii) ATB use outside the ICI treatment window (defined as within 60 days before or after ICI administration, a period that encompasses the post-antibiotic effects of most ATBs) [18, 19]. Based on whether ATBs were used within the ICI treatment window, patients were divided into two groups: the Antibiotic Group (ATB group) and the Non-Antibiotic Group (non-ATB group).

Follow-up

All patients were followed up for survival status and disease progression through telephone interviews or electronic medical records, with the last follow-up date being June 30, 2024. The efficacy evaluation indicators for

cancer patients included OS and PFS. OS was defined as the time from the initial administration of ICIs to death from any cause or the last follow-up date, while PFS was defined as the time from the initial administration of ICIs to clinical disease progression or the last follow-up date.

Statistical analysis

Data were analyzed using SPSS version 22.0. The chi-square test was used to analyze the association between clinical data of the two patient groups. Kaplan-Meier survival models were employed to generate survival curves for OS and PFS, with intergroup differences compared using the log-rank test. Cox proportional hazards models were used to analyze factors affecting survival prognosis. A *p*-value of less than 0.05 was considered statistically significant.

Results

Comparison of clinical characteristics of enrolled patients

A total of 102 patients with advanced HCC who received ICIs treatment were included in this study, with a median age of 62 years. Among them, 29 patients were in the ATB group, and 73 patients were in the non-ATB group. The baseline clinical characteristics of the two groups are presented in Table 1. There were no significant differences between the two groups in terms of gender, age, distant metastasis status, treatment regimens, ECOG performance status, or AFP levels. This indicates that the baseline characteristics of the two groups were balanced, reducing the potential impact of confounding factors on the observed differences in PFS and OS.

Impact of ATBs on prognosis of advanced HCC patients receiving ICIs

The PFS and OS of the two patient groups were evaluated. The results indicated that the ATB group had a significantly shorter median PFS (152.107 days vs. 284.451 days, $P = 0.034$) and median OS (435.893 days vs. 661.618 days, $P = 0.021$) compared to the non-ATB group. These findings suggest that the use of ATBs has a detrimental impact on both PFS and OS in patients with advanced HCC. The survival curves for these patients are shown in Fig. 1.

Univariate and multivariate Cox regression analysis of prognostic factors

Univariate analysis revealed that ATBs use (HR = 1.567, 95% CI: 1.001–2.454, $P = 0.049$) and alpha-fetoprotein (AFP) levels (HR = 1.946, 95% CI: 1.256–3.013, $P = 0.003$) were significantly associated with PFS. Multivariate analysis showed similar results, as detailed in Fig. 2. For OS, gender (HR = 2.015, 95% CI: 1.016–3.997, $P = 0.045$) and ATBs use (HR = 1.795, 95% CI: 1.065–3.024, $P = 0.028$) were significantly associated. Notably, ATBs use was identified as an independent risk factor affecting OS (HR = 1.733, 95% CI: 1.026–2.928, $P = 0.040$), as shown in Fig. 3.

Subgroup analysis

In the ATB group, patients were classified based on the type of ATB intoβ-lactam and non-β-lactam categories; by the reason for ATBs use into pulmonary infection, abdominal infection, bloodstream infection, and other infections; and by the duration of ATBs use into ≤7 days and >7 days. The results showed that within the ATB group, patients with pulmonary infections (median PFS = 92.375 days) had significantly shorter PFS compared to those treated for abdominal infections (median PFS = 187.625 days, $P = 0.037$) and other infections (median PFS = 261.667 days, $P = 0.007$), as detailed in Table 2. However, this difference was no longer significant in the multivariate analysis ($P = 0.123$), likely due to adjustments for other confounding factors within the multivariate model. This suggests that the observed difference in PFS between the two groups may not be solely attributable to the type of infection itself but could also

Table 1 Comparison of clinical data between ATB group and non-ATB group

Characteristic		ATB group ($n = 73$)	non-ATB group ($n = 29$)	χ^2	*P*
Age	<65	57	21	0.371	0.543
	≥65	16	8		
Sex	Male	67	24	1.756	0.185
	Female	6	5		
Metastasis	No	45	20	0.481	0.488
	Yes	28	9		
Treatment	ICIs alone	28	15	1.521	0.217
	ICIs with chemotherapy	45	14		
ECOG	0–1	59	19	2.702	0.100
	2	14	10		
AFP	<400 ng·ml^{-1}	34	13	0.026	0.873
	≥400 ng·ml^{-1}	39	16		

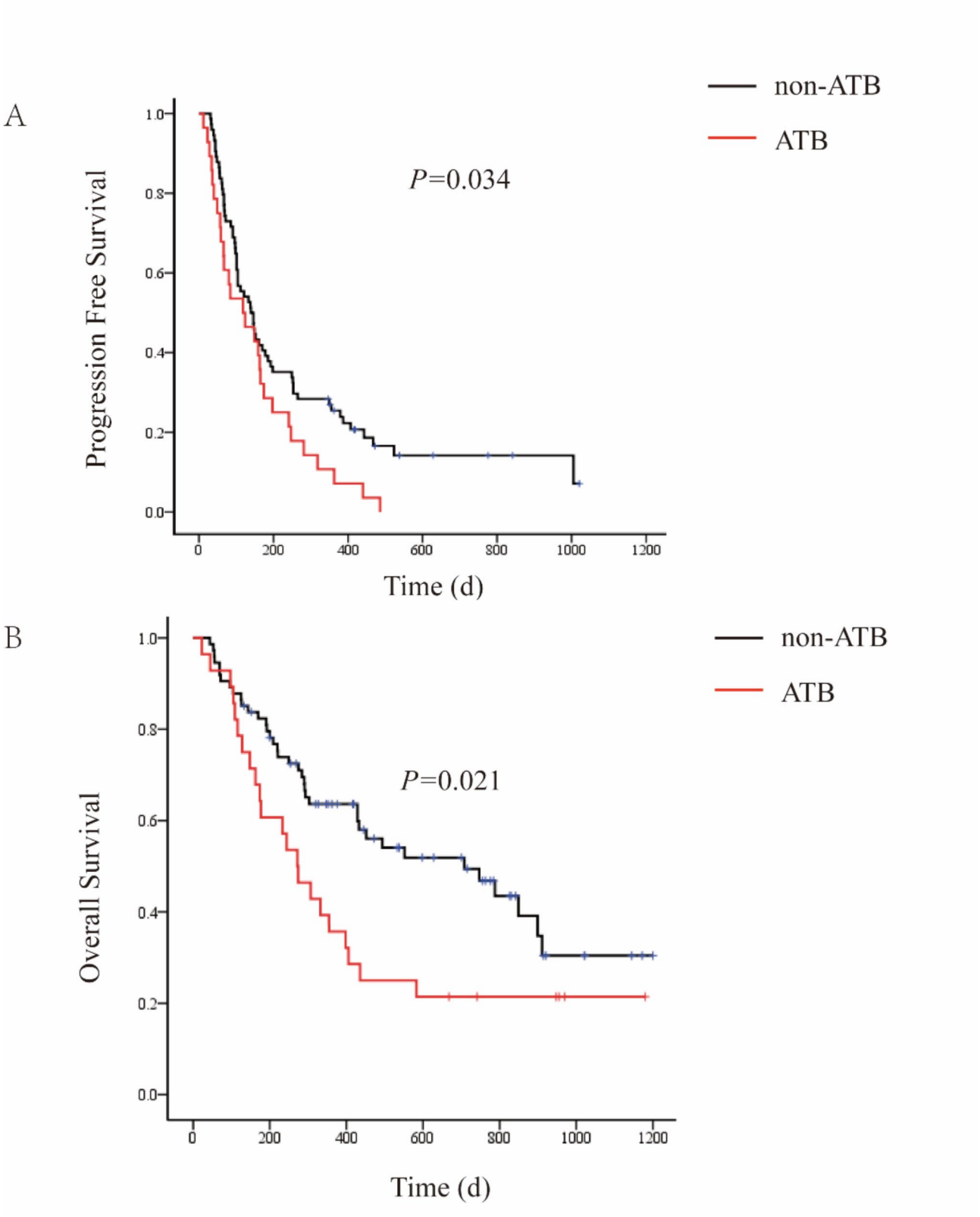

Fig. 1 Survival curves. (**A**) PFS curve in ATB group and non-ATB group. (**B**) OS curve in ATB group and non-ATB group

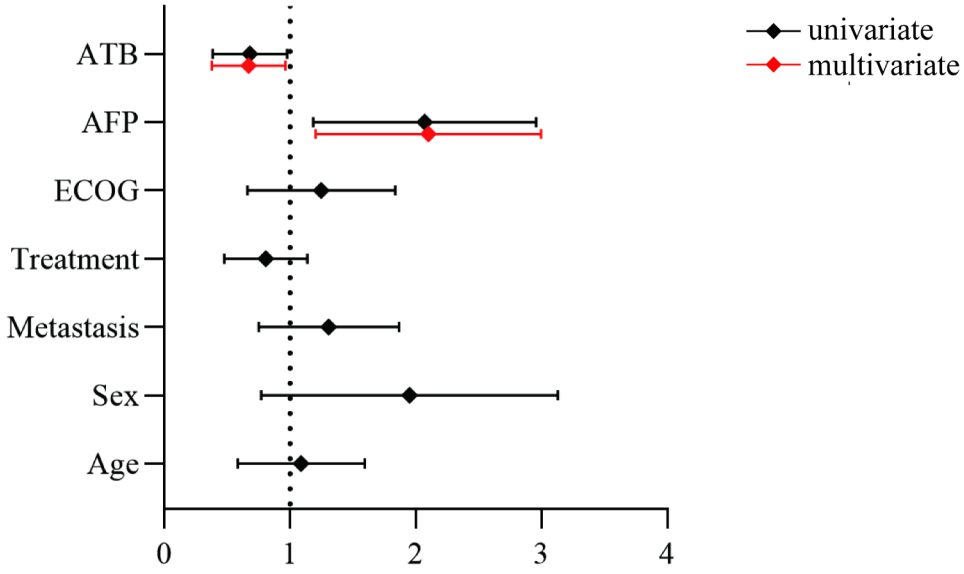

Fig. 2 Univariate and multivariate analysis of PFS in ATB group

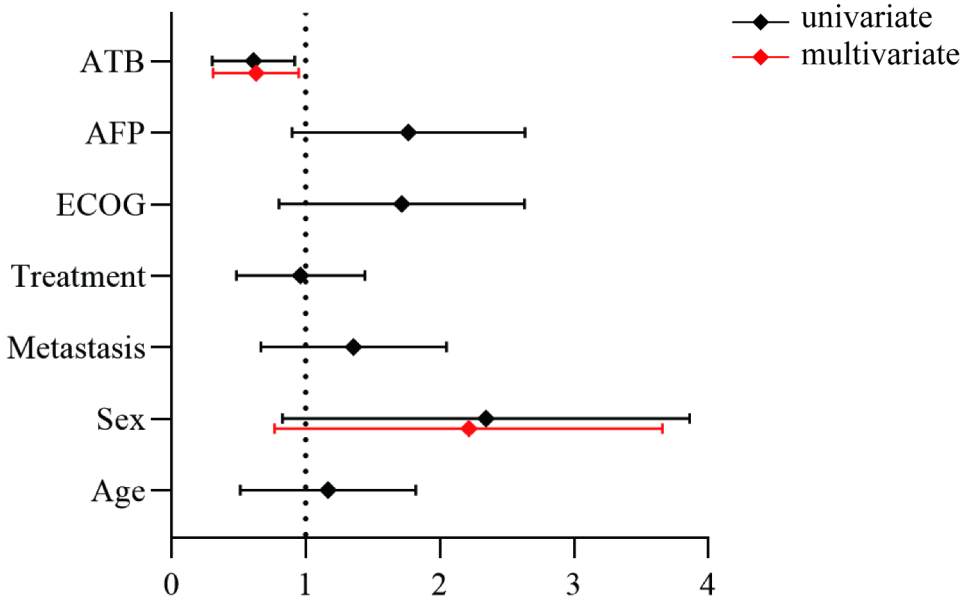

Fig. 3 Univariate and multivariate analysis of OS in ATB group

be influenced by other underlying factors. As shown in Table 3, patients who received ATBs for infections other than pulmonary, abdominal, or bloodstream infections exhibited significantly better OS (HR = 0.252, 95% CI: 0.071–0.889, $P = 0.032$) compared to those with other infection types. This finding indicates that infection type may play a crucial role in the long-term efficacy of immunotherapy. The use of ATBs for other infections ($P = 0.032$) was identified as a potential independent factor affecting OS.

Discussion

Immunotherapy is increasingly playing a crucial role in the treatment of liver cancer. Both domestic drugs such as *teriprizumab*, *sintilimab*, and *camrelizumab*, as well as international drugs like durvalumab and nivolumab, have demonstrated significant efficacy. As the use of ICIs becomes more widespread, understanding drug interactions has become a critical component of comprehensive antitumor treatment management. This study retrospectively analyzed real-world cases from our hospital to explore the impact of ATBs use on the efficacy of immunotherapy in advanced HCC patients. Our findings revealed that among the 102 HCC patients receiving

Table 2 Univariate and multivariate analysis of PFS in ATB group

		Univariate			Multivariate		
	n **= 29**	**HR**	**95%CI**	**P**	**HR**	**95%CI**	**P**
Antibiotic Categories		2.101	0.480–9.204	0.325			
β-lactams	27						
Non-β-lactams	2						
Indications for Antibiotic Use							
Pulmonary infections	8	1.000			1.000		
Intra-abdominal infections	8	0.302	0.098–0.931	0.037	0.406	0.129–1.277	0.123
Bloodstream infections	6	1.169	0.400-3.415	0.775			
Other indications	7	0.201	0.063–0.642	0.007	0.138	0.034–0.554	0.005
Duration of Antibiotic Therapy		0.937	0.394–2.227	0.883			
≤ 7 days	21						
>7 days	8						

Table 3 Univariate analysis of OS in ATB group

		Univariate		
	n **= 29**	**HR**	**95%CI**	**P**
Antibiotic Categories		1.978	0.265–14.787	0.506
β-lactams	27			
Non-β-lactams	2			
Indications for Antibiotic Use				
Pulmonary infections	8	1		
Intra-abdominal infections	8	0.458	0.150–1.401	0.171
Bloodstream infections	6	1.702	0.548–5.288	0.358
Other indications	7	0.252	0.071–0.889	0.032
Duration of Antibiotic Therapy		0.971	0.381–2.427	0.951
≤ 7 days	21			
>7 days	8			

ICIs, significant differences in PFS and OS were observed between the ATB and non-ATB groups. The use of ATBs was identified as a risk factor affecting the efficacy of ICIs.

Kanan et al. collected data from 59 patients to assess the impact of ATBs use on OS in Child-Pugh class A liver cancer patients undergoing ICI therapy. Their results indicated that patients who did not receive ATBs had a significantly longer median OS following PD-1 inhibitor treatment compared to those who received ATBs (22 months vs. 6 months) [20]. This phenomenon is not limited to liver cancer alone; similar findings have been observed in other cancer types. For instance, Derosa et al. found that patients with advanced renal cancer who received ATBs exhibited a higher risk of disease progression (75% vs. 22%), markedly shorter PFS (1.9 months vs. 7.4 months), and significantly reduced OS (17.3 months vs. 30.6 months) compared to those who did not receive ATBs [18]. Additionally, another study across various solid tumors revealed that patients who used ATBs within 60 days prior to ICI therapy had poorer PFS (2 months vs. 4 months) and OS (5 months vs. 17 months) [21]. These findings collectively highlight the potential impact of ATBs use on the efficacy of ICI therapy in cancer treatment.

The interaction between ATBs and ICIs is complex, some studies report results that differ from those found in this study. We propose that the differences in findings may be attributed to several factors: (1) the relatively small sample size in our study may introduce bias and affect the generalizability of the results; (2) variations in the types of malignancies studied across different reports may lead to differing results due to disease-specific characteristics. For instance, research on non-small cell lung cancer by Kaderbhai et al. and Dvid J et al. did not show a significant impact of ATBs use on ICI efficacy [22, 23]. In metastatic renal cell carcinoma, the use of ATBs has been identified as an independent factor associated with poor prognosis following immunotherapy, as well as an increased incidence of immune-related adverse events [24]. The differences in these outcomes may be attributed to variations in the tumor microenvironment and gut microbiota across different tumor types. (3) Different classes of ATBs may have distinct effects on ICIs. Among commonly used ATBs, β-lactams affect a broad spectrum of Enterococci, Enterobacteriaceae, and Gram-positive cocci [25]. Studies have shown that β-lactam-induced alterations in gut microbiota reduce the expression of major histocompatibility complex class I and II genes, leading to changes in the tumor microenvironment and promoting tumor immune evasion [26]. Quinolones, on the other hand, are effective against Ruminococcus, Bifidobacteria, and Alistipes, bacterial genera that have been implicated in influencing ICI efficacy [27, 28]. Additionally, quinolones possess immunomodulatory properties and may impact both cellular and humoral immunity by attenuating cytokine responses [29]. A study by Guerrero et al. demonstrated that broad-spectrum ATBs (defined as those covering Gram-positive, Gram-negative, and/or anaerobic bacteria) significantly affected ICI efficacy, whereas no such effect was observed with narrow-spectrum ATBs (which primarily target Gram-positive

bacteria). Similarly, in a study on non-small cell lung cancer [30]. Qiu et al. found that quinolones did not have a significant negative impact on clinical outcomes, whereas β-lactam ATBs were associated with a significant reduction in OS [31]. Therefore, when interpreting and comparing results from different studies, it is crucial to consider these potential variables and differences to more accurately assess the impact of ATBs use on ICI treatment efficacy.

The specific mechanisms by which ATBs affect the efficacy of ICIs remain to be fully elucidated, but changes in the gut microbiota are considered a key factor. The human gut and mucosal surfaces are home to thousands of commensal bacteria that engage in a symbiotic relationship with the host. Among these, the diversity and abundance of Bifidobacterium and Bacteroides species are thought to influence ICI efficacy [32, 33]. For example, in patients with advanced non-small cell lung cancer receiving ICI therapy, the presence of Akkermansia muciniphila has been associated with a higher objective response rate (ORR) and improved OS [34]. Similarly, in melanoma patients undergoing ICI treatment, prolonged PFS has been linked to higher abundances of Faecalibacterium prausnitzii, Coprococcus eutactus, and Prevotella stercorea, whereas shorter PFS has been associated with increased levels of Bacteroides ovatus, B. dorei, B. massiliensis, Ruminococcus gnavus, and Blautia producta [35]. These findings suggest that specific gut microbiota compositions may play a crucial role in modulating ICI efficacy. The use of ATBs alters both the abundance and diversity of gut bacteria, potentially impacting the therapeutic outcomes of ICIs [36]. Changes in the gut microbiota can induce the production of cytokines such as IL-6, GM-CSF, and TGF-β, which play a role in promoting the tumor inflammatory microenvironment. These cytokines enhance the migration of bone marrow-derived suppressor cells and regulatory T cells to the tumor microenvironment, thereby inhibiting T-cell-mediated tumor clearance [37]. Moreover, key metabolic byproducts of the gut microbiota, such as short-chain fatty acids including butyrate, acetate, and propionate, play a crucial role in immune system regulation, influencing the immune functions of Tregs, Th cells, and CTLs [38]. Studies have shown that butyrate enhances anti-PD-1 therapy efficacy by promoting CD8 + T cell production of tumor-associated cytokines, such as IFN-γ, TNF-α, and IL-2, through TCR-dependent signaling pathways [39]. Additionally, secondary bile acids produced by gut microbiota, such as 3-oxoLCA (3-oxo-lithocholic acid) and isoalloLCA (isoallo-lithocholic acid), can directly regulate adaptive immune cells. Research indicates that 3-oxoLCA inhibits Th17 cell differentiation by binding to RORγt, while isoalloLCA promotes Treg differentiation by inducing mitochondrial reactive oxygen species production. These bile acids may negatively impact ICI efficacy [40]. From a clinical perspective, fecal microbiota transplantation has emerged as a potential strategy to enhance ICI responses. A Phase I clinical trial conducted by Israeli scientists evaluated the effects of FMT combined with reinduction anti-PD-1 immunotherapy in 10 patients with refractory metastatic melanoma. The results demonstrated a significant improvement in immunotherapy response in 3 patients, highlighting the potential of microbiome modulation as an adjunct to ICIs [41]. We hypothesize that alterations in the gut microbiota induced by ATBs may be a potential underlying mechanism for the reduced efficacy of ICI therapy. However, the exact mechanisms remain to be further investigated.

Our results indicate that ATB exposure may be one of the contributing factors to reduced ICI efficacy in clinical practice. However, given that infections are common in patients with advanced HCC and can be life-threatening in severe cases, we do not advocate for the complete avoidance of ATBs. Instead, we recommend a more stringent indication for ATB use, aiming to minimize unnecessary ATB exposure, particularly within the 60-day window before and after the initiation of immunotherapy. When ATBs are necessary, we suggest prioritizing narrow-spectrum ATBs that have a less disruptive impact on gut microbiota to help preserve microbial diversity and mitigate potential negative effects on ICI efficacy.

Despite the rigorous statistical analysis conducted in our study, there are inherent limitations in the research design. First, this study is retrospective in nature, and confounding factors such as the severity of infections or comorbidities inevitably impact the robustness of the results. We adjusted for confounding factors using a multivariate Cox regression model, which helped to mitigate the influence of these factors to some extent. Although we did not directly adjust for patient comorbidities or liver function, we reported baseline characteristics, including the ECOG performance status and AFP levels, which are sensitive indicators of overall health and liver function. In future studies with larger sample sizes, prospective randomized trials or propensity score matching could be employed to further reduce the impact of confounding factor imbalances. Second, while we aimed to perform a more detailed analysis of ATB types and administration routes, the sample size was insufficient to support such in-depth investigation. Lastly, in this study, we handled missing data by excluding patients with incomplete information. While this approach may result in the loss of some patients, the missing data were completely random and relatively minimal, so the impact on result bias is likely to be small. In future research, we aim to conduct a multicenter study with a larger sample size to perform sensitivity analyses. Additionally, we plan to collect stool samples from patients to analyze the gut

microbiota and explore the mechanisms underlying the interaction between ATB and ICIs.

Abbreviations

HCC	Hepatocellular Carcinoma
ATBs	Antibiotics
ICIs	Immune Checkpoint Inhibitors
PFS	Progression-Free Survival
OS	Overall Survival
ECOG	Eastern Cooperative Oncology Group
AFP	Alpha-Fetoprotein
HR	Hazard Ratio
CI	Confidence Interval
FDA	Food and Drug Administration
ORR	Objective Response Rate
DCR	Disease Control Rate
CNLC	China Liver Cancer

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This is not applicable for this study.

Author contributions
Yang LI and Ziwei FENG contributed equally to this work.All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Yang LI, Ziwei FENG and Canhua LIANG. Shaohuan LU and Guangzhao WANG prepared figures and tables. The first draft of the manuscript was written by Yang LI and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
Data are available from the first (corresponding author) upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the principles of the 1964 Declaration of Helsinki and its amendments. It is a retrospective analysis of existing patient data and does not involve any patient harm or human tissue samples. The study has been approved by the Research Ethics Committee of the First People's Hospital of Yulin and has been granted an exemption from informed consent (YLSY-IRB-SR-2023015).

Consent for publication
This is not applicable for this study.

Competing interests
The authors declare no competing interests.

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