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ORIGINAL RESEARCH

The Impact of Proton Pump Inhibitors on the Efficacy of Immune Checkpoint Inhibitor Combinations in Patients with HBV-Associated Advanced Hepatocellular Carcinoma

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Purpose: There is limited research on whether Proton Pump Inhibitors (PPIs) will affect the efficacy of immune checkpoint inhibitors (ICIs) in treating hepatocellular carcinoma (HCC).This study aimed to determine whether PPIs affect the survival outcomes of patients with HBV-associated advanced HCC receiving combination therapy based on ICIs.

Methods: We retrospectively analyzed patients with hepatitis B virus (HBV)-associated advanced HCC who underwent ICIs combination therapy from January 1, 2020, to December 30, 2022. Patients were stratified into PPI and non-PPI groups based on whether they received PPI treatment within 30 days before or after ICIs therapy. Patients' survival and the risk of PPI-associated mortality was assessed. Adverse events were also evaluated.

Results: A total of 183 patients with HBV-associated HCC treated with ICI combination therapy were included. The median survival time (12.5 months vs 13.7 months, $P = 0.285$) and incidence of adverse events ($P = 0.729$) did not significantly differ between the PPI and non-PPI groups. Even after propensity score matching, the difference in median overall survival (OS) between the two groups was not significant (10.7 months vs 11.4 months; $P = 0.596$) and the patient's OS is not significantly related to the dosage of PPI application ($P > 0.05$).However, according to our subgroup analysis, among HCC patients with a serum HBV DNA concentration ≥ 200 IU/mL, the use of PPIs significantly increased the risk of mortality in patients receiving ICI combination therapy ($P = 0.024$).

Conclusion: PPIs do not notably influence the survival prognosis of patients receiving ICI combination therapy for HBV-associated advanced HCC. However, among patients with high levels of HBV DNA, PPIs increase the risk of mortality. Therefore, antiviral therapy should be intensified in the patients with HBVDNA > 200 IU/mL. Additionally, PPIs do not impact the incidence of adverse reactions in these patients.

Keywords: hepatocellular carcinoma, immune checkpoint inhibitors, proton pump inhibitors, chronic hepatitis B virus infection

Introduction

Primary liver cancer is the sixth most prevalent type of cancer globally and is the third leading cause of cancer-related death. Hepatocellular carcinoma (HCC) accounts for the vast majority of cases, and chronic hepatitis B virus (HBV) infection is the primary risk factor for HCC.[1] However, most HCC patients are diagnosed at an advanced stage and miss the opportunity for curative treatment. Presently, therapeutic approaches for advanced or unresectable HCC mainly include local treatments such as transcatheter arterial chemoembolization (TACE), targeted therapies such as tyrosine kinase inhibitors (TKIs), and immune checkpoint inhibitors (ICIs) such as anti-PD-1 monoclonal antibodies. Prior studies have indicated that combination therapy involving ICIs significantly enhances antitumor efficacy and prolongs overall survival (OS) compared to treatments not involving ICIs.[2–5] Consequently, combination therapy based on ICIs has emerged as a primary treatment for advanced HCC. However, the treatment outcomes for most patients are

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unsatisfactory, primarily due to incomplete understanding of the factors influencing the antitumor efficacy of ICIs. Recent research has shown that dysbiosis of the gut microbiota can impact the antitumor efficacy of ICIs.[6] However, it remains unclear whether drugs interfering with the gut microbiota have an effect on the efficacy of ICIs in treating HCC.

Proton pump inhibitors (PPIs), commonly used as acid-suppressive gastroprotective agents, are frequently employed in the treatment of advanced HCC. Studies have suggested that PPIs might affect the antitumor efficacy of ICIs by potentially influencing the balance of the gut microbiota,[7–9] thereby potentially impacting the effectiveness of ICIs. Hopkins et al[10] investigated the impact of PPIs on OS and progression-free survival (PFS) in patients receiving various treatment regimens for non-small cell lung cancer, and the results indicated that PPIs were associated with negative prognostic outcomes in patients receiving regimens containing atezolizumab. Additionally, Rassy et al[11] reported that while the use of PPIs did not affect the OS or PFS of renal cell carcinoma patients receiving ICI treatment, immune-related adverse events were more frequent in patients using PPIs. Recent research investigating whether PPIs or H2 receptor antagonists affect the efficacy of ICI treatment in advanced HCC patients has not shown any detrimental impact of acid-suppressive drugs on the prognosis of HCC patients receiving ICI treatment.[12] However, the precise influence of PPIs on the effectiveness of ICI-based combination therapy for patients with HBV-related advanced HCC has yet to be conclusively established. Thus, this study further analyzed the impact of PPIs on the efficacy of ICIs combinations in patients with HBV-associated advanced HCC.

Materials and Methods

Patient

This study consecutively enrolled Patients with HBV-associated advanced HCC who received ICI treatment at the Affiliated Hospital of Xuzhou Medical University between January 1, 2020, and December 31, 2022. Treatment regimens for patients included combinations of ICIs with TACE plus TKIs, ICIs with TACE, and ICIs with TKIs. The ICIs for treatment included Camrilizumab (Henrui Medicine), Simlizumab (innovative biological agent), and Tislizumab (Beijing), ect, which were administered at a fixed dose of 200 mg every three weeks. In combination therapy, the timing of TACE and embolic agent selection depends on the patient's tumor control and liver function. TKIs, including sorafenib, lenvatinib, apatinib, and anlotinib, were chosen based on the patient's condition and the treatment decision of the attending physician. The inclusion criteria for patients were as follows: 1) aged > 18 years and of any sex; 2) diagnosed with HCC according to the 2022 American Association for the Study of Liver Diseases (AASLD) guidelines; 3) received at least three cycles of ICI treatment; 4) positive for HBV DNA or HBsAg in serum or past HBV infection; 5) Barcelona Clinic Liver Cancer (BCLC) stage B or C; and 6) Child–Pugh class A or B (≤7 points). The exclusion criteria for patients were as follows: 1) survived for less than 3 months; 2) had concomitant other cancers; 3) lacked baseline or follow-up data; and 4) had severe bleeding or infection. This study was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University and was retrospective in nature; therefore, informed consent was not needed.

Study Design and Assessment

We categorized HBV-associated advanced HCC patients into PPI and non-PPI groups based on whether they received PPIs within 30 days before and after initial ICI therapy. The PPIs included omeprazole, pantoprazole, rabeprazole, and others. Patients' OS was evaluated from the initiation of the first ICI treatment to the endpoints of death, last treatment, or study Research deadline. Adverse events were assessed using the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE 5.0).

Data Collection

The clinical data of the patients were obtained from the electronic medical records system of the Affiliated Hospital of Xuzhou Medical University. The retrospective assessment included patient age; sex; HBV DNA, HBsAg, anti-HBs, HBeAg, anti-HBe, and anti-HBc status; liver function; complete blood count; AFP; coagulation function; ICI and PPI

usage; imaging data; and other relevant information. Patient information was updated every three months based on outpatient records, subsequent hospitalizations, and follow-up phone calls.

Statistical Analysis

The statistical analysis was conducted using SPSS 26.0 software. Normally distributed continuous data are presented as the mean ± standard deviation (x ± s) and were compared using the *t*-test. Nonnormally distributed continuous data are presented as medians (P_{25}, P_{75}) and were compared using nonparametric tests. Categorical data are expressed as percentages (%) and were compared using the chi-square test. OS was evaluated, and survival curves were generated using the Kaplan-Meier method, with survival rates compared among different groups using the Log rank test. Propensity score matching (PSM) was performed to overcome baseline imbalances. A P value < 0.05 was considered to indicate statistical significance.

Results

There Was No Difference in Patient Baseline Characteristics After PSM

This study initially included 218 patients with HBV-related advanced HCC receiving ICI treatment. In accordance with the inclusion and exclusion criteria, 19 patients with a survival time less than 3 months, 1 patient with concurrent other cancers, 12 patients lacking baseline or follow-up data, and 3 patients with severe bleeding or infection were excluded, resulting in a final cohort of 183 patients being included in the study (Figure 1). The baseline characteristics of the enrolled patients are presented in Table 1. In all of the enrolled patients, 88 had used PPIs within 1 month before and after the start of treatment, and the median duration of PPIs was 7 days. These patients used PPIs to improve digestive symptoms possibly caused by cancer, or to alleviate gastrointestinal reactions perhaps resulted from treatment. There was a significant difference in baseline albumin levels between the two groups of patients treated with and without PPIs (Table 1). To minimize the potential impact of confounding factors, a 1:1 propensity score matching was performed considering variables such as age, sex, treatment modality, alcohol history, Child-Pugh classification, BCLC stage, HBV DNA viral load, antiviral status, alanine aminotransferase, aspartate aminotransferase, total bilirubin, albumin, prothrombin time, white blood cell count, platelet count, and alpha-fetoprotein levels. A total of 60 patient pairs were successfully

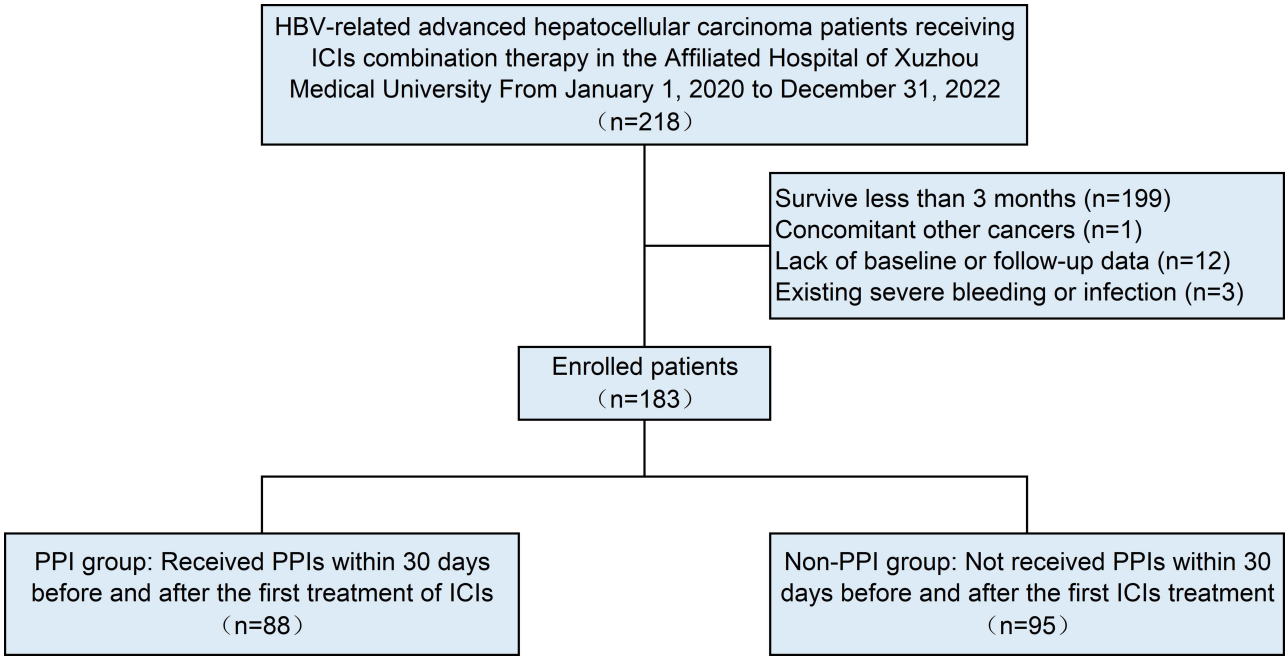

Figure 1 The patients flowchart.
Abbreviations: ICIs, immune checkpoint inhibitors; PPI, Proton pump inhibitors; HBV, Hepatitis B virus.

Table 1 Baseline Characteristics of Patients Before and After Propensity Matching

Variable	Before PSM				After PSM			
	Total (n = 183)	Non-PPI (n = 95)	PPI (n =88)	P	Total (n = 120)	Non-PPI (n = 60)	PPI (n = 60)	P
AGE, years	56.85 ± 10.40	56.91 ± 10.12	56.78 ± 10.76	0.937[a]	57.66 ± 9.89	57.83 ± 9.43	57.48 ± 10.41	0.847[a]
SEX, n (%)				0.366[b]				0.769[b]
Male	164 (89.62)	87 (91.58)	77 (87.50)		107 (89.17)	53 (88.33)	54 (90.00)	
Female	19 (10.38)	8 (8.42)	11 (12.50)		13 (10.83)	7 (11.67)	6 (10.00)	
History of alcoholism, n (%)				0.094[b]				0.658[b]
No	139 (75.96)	77 (81.05)	62 (70.45)		94 (78.33)	48 (80.00)	46 (76.67)	
Yes	44 (24.04)	18 (18.95)	26 (29.55)		26 (21.67)	12 (20.00)	14 (23.33)	
Child-Pugh, n (%)				0.88[b]				0.637[b]
A	151 (82.51)	78 (82.11)	73 (82.95)		98 (81.67)	48 (80.00)	50 (83.33)	
B	32 (17.49)	17 (17.89)	15 (17.05)		22 (18.33)	12 (20.00)	10 (16.67)	
BCLC, n (%)				0.326[b]				0.714[b]
B	95 (51.91)	46 (48.42)	49 (55.68)		64 (53.33)	33 (55.00)	31 (51.67)	
C	88 (48.09)	49 (51.58)	39 (44.32)		56 (46.67)	27 (45.00)	29 (48.33)	
Antiviral therapy, n (%)				0.947[b]				0.783[b]
Yes	164 (89.62)	85 (89.47)	79 (89.77)		105 (87.5)	52 (86.67)	53 (88.33)	
No	19 (10.38)	10 (10.53)	9 (10.23)		15 (12.5)	8 (13.33)	7 (11.67)	
Treatment, n (%)				0.48[b]				0.477[b]
TACE+ICIs+TKIs	124 (67.76)	62 (65.26)	62 (70.45)		83 (69.17)	43 (71.67)	40 (66.67)	
ICIs+TKIs	38 (20.77)	23 (24.21)	15 (17.05)		25 (20.83)	13 (21.67)	12 (20.00)	
TACE+ICIs	21 (11.48)	10 (10.53)	11 (12.50)		12 (10)	4 (6.67)	8 (13.33)	
HBVDNA, n (%)				0.183[b]				1[b]
<200IU/mL	109 (59.56)	61 (64.21)	48 (54.55)		74 (61.67)	37 (61.67)	37 (61.67)	
≥200IU/mL	74 (40.44)	34 (35.79)	40 (45.45)		46 (38.33)	23 (38.33)	23 (38.33)	
AFP, n (%)				0.228[b]				0.583[b]
<400ng/mL	102 (55.74)	57 (60.00)	45 (51.14)		65 (54.17)	34 (56.67)	31 (51.67)	
≥400ng/mL	81 (44.26)	38 (40.00)	43 (48.86)		55 (45.83)	26 (43.33)	29 (48.33)	
ALT, U/L	36.00 (24.50, 54.00)	34.00 (24.00, 54.00)	39.00 (25.75, 54.00)	0.361[c]	35.50 (24.00, 52.25)	34.50 (23.75, 51.00)	39.00 (24.75, 52.25)	0.562[c]
AST, U/L	45.00 (31.00, 63.50)	42.00 (30.50, 62.50)	49.00 (32.00, 65.75)	0.213[c]	42.00 (30.00, 63.00)	42.00 (32.50, 60.50)	44.00 (29.00, 63.00)	0.852[c]
TBIL, umol/L	17.30 (12.95, 24.95)	17.30 (12.90, 25.70)	17.35 (13.23, 24.33)	0.848[c]	17.40 (12.97, 24.42)	16.35 (12.90, 23.00)	18.90 (13.23, 24.90)	0.467[c]
ALB, g/L	38.75 ± 5.34	39.94 ± 5.48	37.47 ± 4.90	0.002[a]	38.95 ± 4.77	38.80 ± 5.15	39.10 ± 4.38	0.736[a]
PT, sec	12.30 (11.70, 13.30)	12.30 (11.70, 13.50)	12.30 (11.70, 13.30)	0.547[c]	12.30 (11.70, 13.33)	12.30 (11.70, 13.30)	12.25 (11.78, 13.50)	0.998[c]
WBC, ×109/L	4.90 (3.85, 6.60)	4.90 (4.05, 6.60)	4.90 (3.50, 6.70)	0.541[c]	4.75 (3.77, 6.00)	4.65 (3.77, 5.55)	4.85 (3.85, 6.40)	0.33[c]
NLR, n (%)				0.896[b]				0.187[b]
<2.5	57 (31.15)	30 (31.58)	27 (30.68)		45 (37.5)	26 (43.33)	19 (31.67)	
≥2.5	126 (68.85)	65 (68.42)	61 (69.32)		75 (62.5)	34 (56.67)	41 (68.33)	
PLT, ×109/L	129.00 (83.50, 182.50)	131.00 (87.50, 195.50)	123.50 (81.00, 175.50)	0.382[c]	129.50 (86.00, 183.00)	126.50 (86.00, 199.00)	132.00 (86.75, 175.50)	0.821[c]

matched, and after postmatching there was no significant differences in baseline characteristics between the two groups (Table 1). The types of PPIs used by the patients and the total dose consumed are summarized in Table 2. All patients were treated with proton pump inhibitors with the same mechanism of action, including Omeprazole, Pantoprazole, etc.

PPIs Do Not Affect the Patients' OS

Before matching, the median follow-up duration for the entire cohort was 21.3 months, the median survival time was 13.1 months, and a total of 118 deaths occurred during the follow-up period. The median survival time was 12.5 months for patients in the PPI group and 13.7 months for patients in the non-PPI group; these two groups were not significantly different ($P = 0.285$) (Figure 2A). After matching, the median follow-up duration for the entire cohort was 22.0 months, with a median survival time of 11.4 months. Moreover, there was no significant difference in the median survival time between the PPI and non-PPI groups (10.7 months vs 11.4 months; $P = 0.596$) (Figure 2B). To further analyze the impact of different doses of PPIs on patients' survival time, we divided the patients into three groups: < 200mg, 200–400mg, and > 400mg for survival analysis. The Results showed no significant difference in survival time among the three groups, both before (14.8 months vs 13.5 months vs 6.4 months, $P = 0.285$) (Figure 2C) and after PSM (14.8 months vs 11.6 months vs 6.4 months, $P = 0.804$) (Figure 2D). This suggests that the use of PPIs dose not affect the OS of patients receiving combination therapy with ICIs, and that the dosage of PPIs ingested does not impact patients' survival.

PPIs Increase the Risk of Death in Patients with High Level HBV DNA

Before or after PSM, the use of PPIs did not increase or decrease the risk of death ($P = 0.286$, $P = 0.603$). Subgroup analyses were performed based on age group, sex, treatment modality, Child-Pugh classification, BCLC stage, viral load, and AFP level. The results showed that the use of PPIs neither increased nor reduced the risk of death in different age, sex, treatment modality, Child-Pugh classification, BCLC stage, viral load, and AFP level subgroups before PSM ($P > 0.05$) (Figure 3A). After PSM, PPI usage results in a significant increase in the risk of mortality among patients with HBV DNA levels ≥ 200 IU/mL (HR = 2.170; 95% *CI* 1.106–4.258; $P = 0.024$). However, the impact of PPI usage on the risk of mortality was not significantly evident in the remaining subgroups (Figure 3B).

Adverse Events Were Similar Between the Patients with or Without PPIs

During the treatment process, a total of 133 patients (76.7%) experienced adverse reactions. There was no significant difference in the incidence of adverse reactions between the PPI and non-PPI groups before or after matching (73.9% vs 71.6%, $P = 0.729$; 75.0% vs 70.0%, $P = 0.540$). Similarly, for adverse reactions classified as Grade 3–4, there was no statistically significant difference between the PPI and Non-PPI groups, both before and after matching (8.0% vs 8.4%, $P = 0.908$; 8.3% vs 6.7%, $P = 1.000$) (Table 3).

Table 2 PPIs Use in Patients Before and After Matching

PPIs	Before PSM (n =88)	After PSM (n = 60)
Omeprazole	36 (40.91%)	24 (40.00%)
Esomeprazole	10 (11.36%)	7 (11.67%)
Pantoprazole	13 (14.77%)	6 (10.00%)
Rabeprazole	4 (4.55%)	3 (5%)
Lansoprazole	2 (2.27%)	2 (3.33%)
Two or more PPIs	23 (26.14%)	18 (30.00%)
PPIs dosage		
< 200mg	28 (31.82%)	17 (28.33%)
200–400mg	32 (36.36%)	24 (40.00%)
> 400mg	28 (31.82%)	19 (31.67%)

Abbreviations: PSM, Propensity score matching; PPI, Proton pump inhibitors.

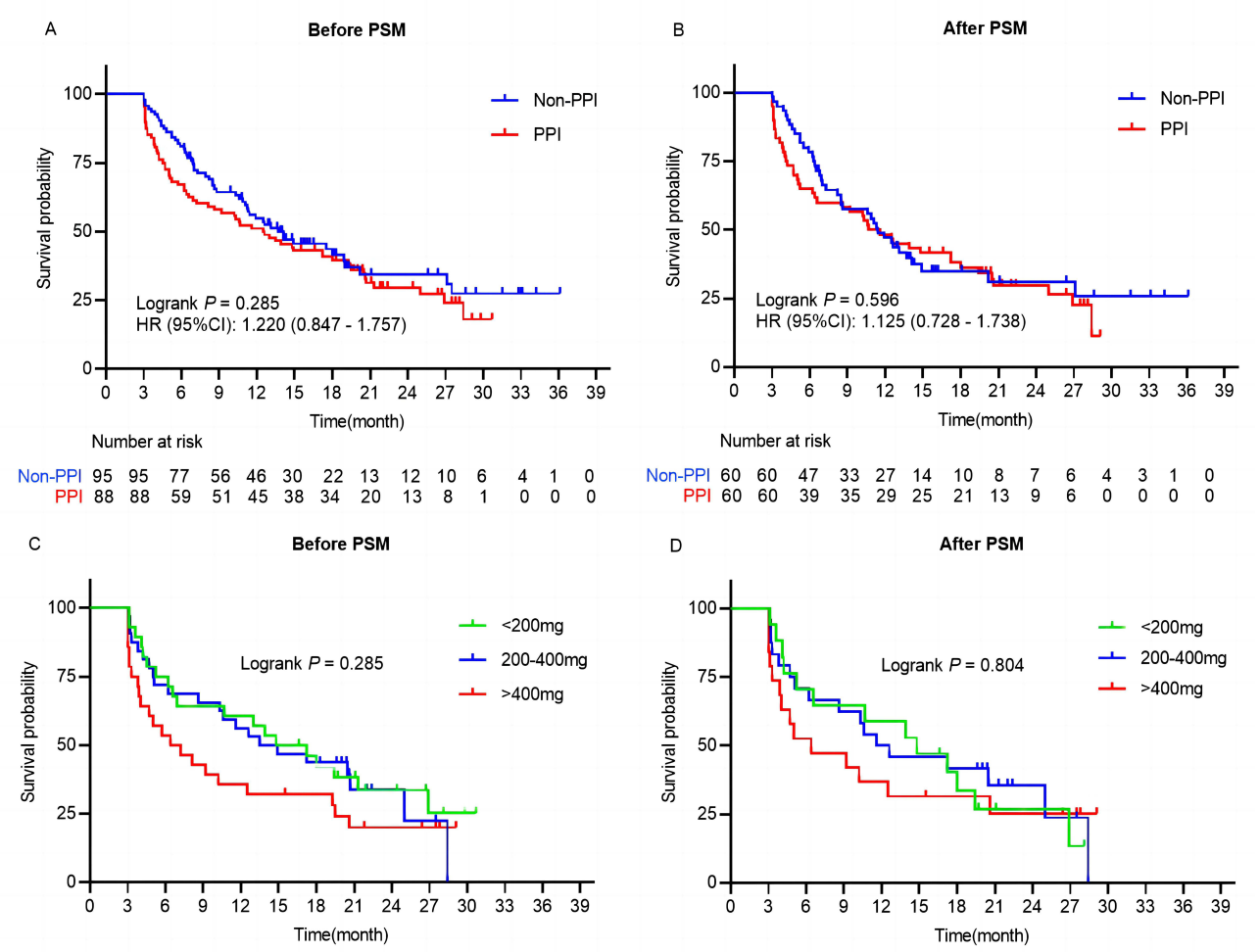

Figure 2 (**A**) Kaplan-Meier curves for patients with and without PPIs before PSM. (**B**) Kaplan-Meier curves for patients with and without PPIs after PSM. (**C**) Kaplan-Meier curves for patients with different PPIs doses before PSM. (**D**) Kaplan-Meier curves for patients with different PPIs doses after PSM.
Abbreviations: PPI, Proton pump inhibitors; PSM, Propensity score matching.

Discussion

Immune checkpoint inhibitors, including cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitors and programmed cell death protein-1 (PD-1) / programmed cell death ligand-1 (PD-L1) inhibitors, mainly modulate T-cell activity and function, activating the body's immune response to exert antitumor effects.[13,14] While the application of ICIs significantly improves clinical outcomes for some cancer patients, including those with liver cancer, the majority of ICIs do not achieve satisfactory outcomes. The exploration of the factors that affect the efficacy of ICIs in tumor therapy has become a hot research topic in this field. Reports suggest that baseline concomitant medications might alter the antitumor effects of ICIs. A multicenter retrospective study analyzing medications taken by patients with cancers such as non-small cell lung cancer, melanoma, and renal cell carcinoma at the beginning of immunotherapy revealed a strong correlation between the use of antibiotics or PPIs and poorer clinical outcomes with PD-1/PD-L1 checkpoint inhibitors.[15] Several meta-analyses suggest a potential association between PPI use and adverse outcomes in tumor patients treated with ICIs.[16–18] The underlying mechanism may involve PPI-induced alterations in the gut microbiota balance.[19] Clooney et al[20] analyzed stool samples from 61 individuals who did or did not use PPIs and observed a decrease in Bacteroidetes and an increase in Firmicutes at the phylum level in PPI users. Imhann et al[9] analyzed stool samples from 1815 individuals and reported that the diversity of the intestinal microbiota in PPI users was significantly lower than that in nonusers; additionally, species of oral bacteria (such as Rothia) were more abundant in the gut microbiota of PPI users, and the genera Enterococcus, Streptococcus, Staphylococcus and potentially pathogenic *Escherichia coli* were

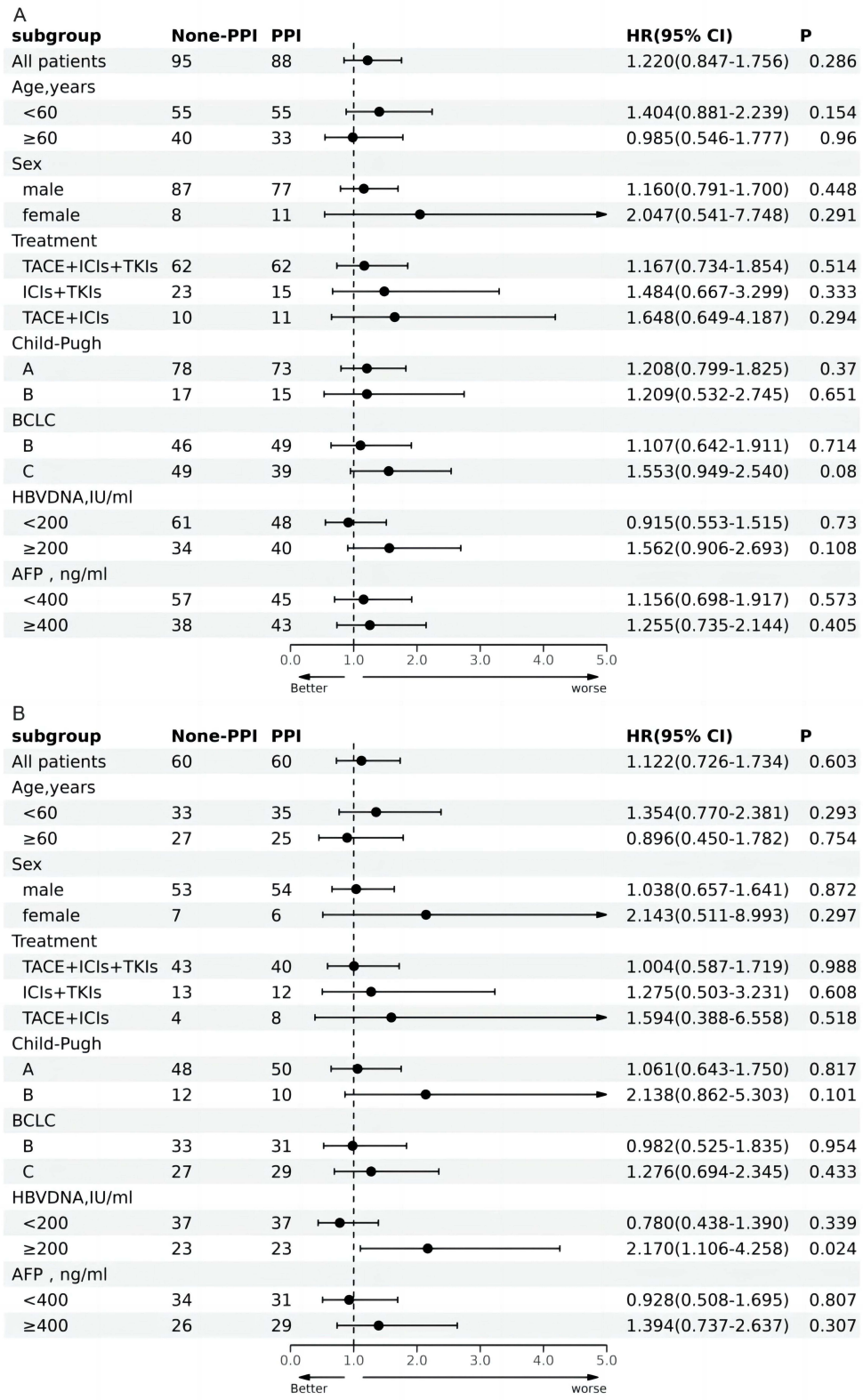

Figure 3 Subgroup analysis of mortality risk for PPI use. (**A**) Before PSM. (**B**) After PSM.

Abbreviations: TACE+ICIs+TKIs, Transarterial chemoembolization combined with immune checkpoint inhibitors plus tyrosine kinase inhibitors; ICIs+TKIs, Immune checkpoint inhibitors combined with tyrosine kinase inhibitors; TACE+ICIs, Transarterial chemoembolization combined with immune checkpoint inhibitors; PSM, Propensity score matching; BCLC, Barcelona Clinic Liver Cancer; HBV DNA, Hepatitis B virus deoxyribonucleic acid; AFP, alpha fetoprotein.

Table 3 Occurrence of Adverse Events

Adverse Effects	Before PSM		After PSM	
	PPI Use 1~2G/3~4G	Non-PPI Use 1~2G/3~4G	PPI Use 1~2G/3~4G	Non-PPI Use 1~2G/3~4G
Increased ALT/AST	36/6	45/7	25/4	28/3
Fever	3/0	4/0	3/0	2/0
Fatigue	12/0	14/0	11/0	10/0
Decreased appetite	16/0	15/0	12/0	10/0
Diarrhea	12/1	10/1	9/1	3/1
Abdominal distension	5/0	5/0	4/0	4/0
Rash	7/0	1/0	6/0	3/0
Itching	4/0	2/0	2/0	2/0
Hypertension	2/0	3/0	2/0	1/0
Desquamate	4/0	1/0	4/0	1/0
Hypothyroidism	4/0	1/0	4/0	0/0
Hyperthyroidism	1/0	0/0	1/0	0/0
Myocarditis	1/0	2/0	1/0	1/0

Abbreviations: PPI, Proton pump inhibitors; PSM, Propensity score matching; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase.

significantly more abundant in PPI users. Taken together, these findings demonstrate that PPI use significantly affects the gut microbiota, and an increasing number of studies indicate the significant impact of the gut microbiota on the antitumor efficacy of ICIs.[7,21] However, a study by Jun et al[12] investigated whether the baseline use of PPIs or H2 receptor antagonists (H_2RAs) affects the efficacy and prognosis of HCC patients receiving ICI treatment. The results indicated that baseline exposure to PPIs/H_2RAs was not associated with overall survival rate, tumor remission rate, or adverse event occurrence. Our study did not demonstrate a significant impact of PPI use on the survival period of HCC patients treated with ICIs, which aligns with prior research on HCC. The influence of PPIs on the prognosis of HCC patients receiving ICI treatment differs from the results observed in patients with nonhepatic tumors. This discrepancy might be due to the fact that HCC patients often have chronic liver diseases such as hepatitis and cirrhosis, which can cause an imbalance in the gut microbiota,[22–24] so that the impact of PPIs on the gut microbiota might not be substantial enough to affect the efficacy of ICIs. However, the exact underlying mechanisms need further exploration.

The results of this study did not show that PPIs had a significant effect on the OS of HCC patients receiving ICI combination therapy. However, upon further subgroup analysis, we observed a significant increase in the risk of death among HCC patients with HBV DNA levels ≥ 200 IU/mL compared to those with serum HBV DNA levels < 200 IU/mL. Zhou et al[25] indicated that changes in the composition of gut microbiota can affect the host's clearance of HBV, which lead to persistent presence of HBV. PPIs may promote persistent HBV infection by altering the gut microbiota. However, hepatitis B virus infection is often associated with a worse prognosis for liver cancer. A study investigating whether HBV DNA and HBsAg levels influence the efficacy of ICIs in HBV-associated HCC patients indicated that high levels of HBV DNA or HBsAg might imply a poorer antitumor response and shorter survival time.[26] The poorer OS observed in HCC patients with high levels of HBV DNA might be associated with active viral replication, excessive depletion of specific CD4+ and CD8+ T cells, and other factors.[27] In the case of high HBV DNA levels, the exact mechanism by which PPIs inhibit the efficacy of ICIs in combination therapy for HCC requires further investigation.

Additionally, this study revealed no significant difference in the occurrence of adverse reactions during the course of ICI combined therapy between the PPI and non-PPI groups, consistent with the findings of several other studies.[28–30] However, other studies have reported an association between the use of PPIs and an increased incidence of adverse reactions related to ICIs.[11,31] The relationship between PPIs and the occurrence of immune-related adverse events in patients remains inconclusive. Considering the varied adverse reactions caused by different medications, further research

with an expanded sample size or subgrouping based on different drugs is necessary for a more comprehensive understanding of the disease.

This study has several limitations. First, this was a retrospective study conducted at a single center with a relatively small sample size. Second, despite the propensity score matching conducted in this study, there is still a possibility of bias. Future investigations should focus on expanding the sample size and conducting prospective studies to further validate the findings presented in this study.

In conclusion, this study revealed no significant impact of PPIs on the OS of patients with HBV-associated advanced HCC treated with a combination of ICIs. However, for patients with HBV DNA levels ≥ 200 IU/mL, the use of PPIs might increase the risk of patient mortality. This further emphasizes the significance of anti-HBV therapy during ICI treatment for HBV-associated HCC. Additionally, the use of PPIs did not significantly affect the occurrence rate of immune-related adverse events.

Conclusion

PPIs do not notably influence the survival prognosis of patients receiving ICI therapy for HBV-associated advanced HCC. However, among patients with high levels of HBV DNA, PPIs increase the risk of mortality. Additionally, PPIs do not impact the incidence of adverse reactions in these patient.

Data Sharing Statement

The datasets analyzed in this study are available from the corresponding authors upon reasonable request.

Ethics Approval and Informed Consent

The studies were reviewed and approved by The ethics committee of Xuzhou Medical University Affiliated Hospital (Ethics number: xyfy2022-KL085-01). This study is a retrospective observational study, which does not interfere with the patient's treatment plan and the patient's information is anonymous, so written informed consent is not required. We confirm that this study was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki.

Consent to Publish

The manuscript does not involve any form of data containing personal details.

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Author Contributions

All authors contributed to the study, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; participated in the drafting or writing the article, or substantially revised or critically reviewed the article; read and approved the final manuscript. Agreed on the journal to which the article will be submitted; all versions of the article at each stage are reviewed and agreed upon. And agree to take responsibility and be accountable for the contents of the article.

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The authors have no relevant financial or non-financial interests to disclose for this work.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. Chen S, Wu Z, Shi F, et al. Lenvatinib plus TACE with or without pembrolizumab for the treatment of initially unresectable hepatocellular carcinoma harbouring PD-L1 expression: a retrospective study. *J Cancer Res Clin Oncol*. 2022;148(8):2115–2125. doi:10.1007/s00432-021-03767-4
3. Han Z, Yang F, Zhang Y, et al. Prognostic efficacy and prognostic factors of TACE plus TKI with ICIs for the treatment of unresectable hepatocellular carcinoma: a retrospective study. *Front Oncol*. 2022;12:1029951. doi:10.3389/fonc.2022.1029951
4. Wang WJ, Liu ZH, Wang K, et al. Efficacy and safety of TACE combined with lenvatinib and PD-1 inhibitors for unresectable recurrent HCC: a multicenter, retrospective study. *Cancer Med*. 2023;12(10):11513–11524. doi:10.1002/cam4.5880
5. Cai M, Huang W, Huang J, et al. Transarterial chemoembolization combined with lenvatinib plus PD-1 inhibitor for advanced hepatocellular carcinoma: a retrospective cohort study. *Front Immunol*. 2022;13:848387. doi:10.3389/fimmu.2022.848387
6. Lee PC, Wu CJ, Hung YW, et al. Gut microbiota and metabolites associate with outcomes of immune checkpoint inhibitor-treated unresectable hepatocellular carcinoma. *J Immunother Cancer*. 2022;10(6):e004779. doi:10.1136/jitc-2022-004779
7. Derosa L, Routy B, Desilets A, et al. Microbiota-centered interventions: the next breakthrough in immuno-oncology. *Cancer Discov*. 2021;11(10):2396–2412. doi:10.1158/2159-8290.CD-21-0236
8. Imhann F, Vich Vila A, Bonder MJ, et al. The influence of proton pump inhibitors and other commonly used medication on the gut microbiota. *Gut Microbes*. 2017;8(4):351–358. doi:10.1080/19490976.2017.1284732
9. Imhann F, Bonder MJ, Vich Vila A, et al. Proton pump inhibitors affect the gut microbiome. *Gut*. 2016;65(5):740–748. doi:10.1136/gutjnl-2015-310376
10. Hopkins AM, Kichenadasse G, McKinnon RA, et al. Efficacy of first-line atezolizumab combination therapy in patients with non-small cell lung cancer receiving proton pump inhibitors: post hoc analysis of IMpower150. *Br J Cancer*. 2022;126(1):42–47. doi:10.1038/s41416-021-01606-4
11. Rassy E, Dalban C, Colomba E, et al. Efficacy and safety of concomitant proton pump inhibitor and nivolumab in renal cell carcinoma: results of the GETUG-AFU 26 NIVOREN multicenter Phase II study. *Clin Genitourin Cancer*. 2022;20(5):488–494. doi:10.1016/j.clgc.2022.07.003
12. Jun T, Ozbek U, Dharmapuri S, et al. Antacid exposure and immunotherapy outcomes among patients with advanced hepatocellular carcinoma. *Ther Adv Med Oncol*. 2021;13:17588359211010937. doi:10.1177/17588359211010937
13. Delmas D, Hermetet F, Aires V. PD-1/PD-L1 checkpoints and resveratrol: a controversial new way for a therapeutic strategy. *Cancers*. 2021;13(18):4509. doi:10.3390/cancers13184509
14. Zhang H, Dai Z, Wu W, et al. Regulatory mechanisms of immune checkpoints PD-L1 and CTLA-4 in cancer. *J Exp Clin Cancer Res*. 2021;40(1):184. doi:10.1186/s13046-021-01987-7
15. Cortellini A, Tucci M, Adamo V, et al. Integrated analysis of concomitant medications and oncological outcomes from PD-1/PD-L1 checkpoint inhibitors in clinical practice. *J Immunother Cancer*. 2020;8(2):e001361. doi:10.1136/jitc-2020-001361
16. Lopes S, Pabst L, Dory A, et al. Do proton pump inhibitors alter the response to immune checkpoint inhibitors in cancer patients? A meta-analysis. *Front Immunol*. 2023;14:1070076. doi:10.3389/fimmu.2023.1070076
17. Qin BD, Jiao XD, Zhou XC, et al. Effects of concomitant proton pump inhibitor use on immune checkpoint inhibitor efficacy among patients with advanced cancer. *Oncoimmunology*. 2021;10(1):1929727. doi:10.1080/2162402X.2021.1929727
18. Chen B, Yang C, Dragomir MP, et al. Association of proton pump inhibitor use with survival outcomes in cancer patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis. *Ther Adv Med Oncol*. 2022;14:17588359221111703. doi:10.1177/17588359221111703
19. Malfertheiner P, Kandulski A, Venerito M. Proton-pump inhibitors: understanding the complications and risks. *Nat Rev Gastroenterol Hepatol*. 2017;14(12):697–710. doi:10.1038/nrgastro.2017.117
20. Clooney AG, Bernstein CN, Leslie WD, et al. A comparison of the gut microbiome between long-term users and non-users of proton pump inhibitors. *Aliment Pharmacol Ther*. 2016;43(9):974–984. doi:10.1111/apt.13568
21. Zhou CB, Zhou YL, Fang JY. Gut microbiota in cancer immune response and immunotherapy. *Trends Cancer*. 2021;7(7):647–660. doi:10.1016/j.trecan.2021.01.010
22. Yamamoto K, Ishigami M, Honda T, et al. Influence of proton pump inhibitors on microbiota in chronic liver disease patients. *Hepatol Int*. 2019;13(2):234–244. doi:10.1007/s12072-019-09932-9
23. Joo EJ, Cheong HS, Kwon MJ, Sohn W, Kim HN, Cho YK. Relationship between gut microbiome diversity and hepatitis B viral load in patients with chronic hepatitis B. *Gut Pathog*. 2021;13(1):65. doi:10.1186/s13099-021-00461-1
24. Zhu Q, Xia P, Zhou X, et al. Hepatitis B virus infection alters gut microbiota composition in mice. *Front Cell Infect Microbiol*. 2019;9:377. doi:10.3389/fcimb.2019.00377
25. Zhou W, Luo J, Xie X, et al. Gut microbiota dysbiosis strengthens Kupffer cell-mediated hepatitis B virus persistence through inducing endotoxemia in mice. *J Clin Transl Hepatol*. 2022;10(1):17–25. doi:10.14218/JCTH.2020.00161
26. Pan S, Yu Y, Wang S, et al. Correlation of HBV DNA and hepatitis B surface antigen levels with tumor response, liver function and immunological indicators in liver cancer patients with HBV infection undergoing PD-1 inhibition combinational therapy. *Front Immunol*. 2022;13:892618. doi:10.3389/fimmu.2022.892618
27. Kalathil SG, Thanavala Y. Natural killer cells and T cells in hepatocellular carcinoma and viral hepatitis: current status and perspectives for future immunotherapeutic approaches. *Cells*. 2021;10(6):1332. doi:10.3390/cells10061332
28. Deng R, Zhang H, Li Y, Shi Y. Effect of antacid use on immune checkpoint inhibitors in advanced solid cancer patients: a systematic review and meta-analysis. *J Immunother*. 2023;46(2):43–55. doi:10.1097/CJI.0000000000000442
29. Miura K, Sano Y, Niho S, et al. Impact of concomitant medication on clinical outcomes in patients with advanced non-small cell lung cancer treated with immune checkpoint inhibitors: a retrospective study. *Thorac Cancer*. 2021;12(13):1983–1994. doi:10.1111/1759-7714.14001
30. Giordan Q, Salleron J, Vallance C, Moriana C, Clement-Duchene C. Impact of antibiotics and proton pump inhibitors on efficacy and tolerance of anti-PD-1 immune checkpoint inhibitors. *Front Immunol*. 2021;12:716317. doi:10.3389/fimmu.2021.716317
31. Kostine M, Mauric E, Tison A, et al. Baseline co-medications may alter the anti-tumoural effect of checkpoint inhibitors as well as the risk of immune-related adverse events. *Eur J Cancer*. 2021;157:474–484. doi:10.1016/j.ejca.2021.08.036