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Original Article

Prophylactic antibiotic use is associated with better clinical outcomes in gastric cancer patients receiving immunotherapy

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Abstract

Background: The relationship between antibiotic treatment and immunotherapy efficacy is complex.

Methods: This study was a single-center study. History of antibiotic use in gastric cancer (GC) patients within 1 or 3 months prior to immunotherapy was collected. Patients were categorized into 3 groups according to whether they had used antibiotics prior to immunotherapy: none, prophylactic use, and infection.

Results: A total of 252 GC patients received immunotherapy, of which 38.5% (97/252) received antibiotic treatment within 1 month before immunotherapy (prophylactic use in 72.2% of patients) and 48.8% (123/252) received antibiotic treatment within 3 months before immunotherapy (prophylactic use in 74.8% of patients). The prophylactic use of antibiotic within 1 month prior to immunotherapy significantly improved overall survival (OS) compared with patients who received anti-infective therapy and had no history of antibiotic use (prophylactic vs infection: OS, 22.6 vs 9.7 m, HR, 0.53, 95% CI, 0.27-1.07; prophylactic vs none: OS, 22.6 vs 14.7 m, HR, 0.57; 95% CI, 0.39-0.83). The use of antibiotics in infected patients did not increase the risk of death in patients compared with those who did not use antibiotics. Prophylactic antibiotic use within 1 month before immunotherapy is an independent prognostic factor for OS.

Conclusions: Prophylactic use of antibiotics is associated with better prognosis in GC patients receiving immunotherapy. Therefore, there is no necessity to delay the use of immune checkpoint inhibitors in this group of patients.

Key words: gastric cancer; antibiotic; immunotherapy; prognosis.

Implications for Practice

Currently, the impact of antibiotics on the effectiveness of immunotherapy is controversial. This study grouped patients based on the reasons for using antibiotics, and the results showed that prophylactic use of antibiotics does not increase the risk of death for patients. Therefore, patients who receive prophylactic antibiotic treatment in clinical practice do not need to delay their immunotherapy.

Introduction

Immunotherapy is an emerging treatment that controls tumor growth by blocking signal transduction between tumor cells and immune cells.[1] Although single-agent immunotherapy is not highly effective in most tumors,[2] a growing number of studies have confirmed that combining immunotherapy with other therapies, such as chemotherapy and antiangiogenesis, can significantly improve patients' objective response rate and survival.[3,4] The results of CheckMate 649, ORIENT-16, and KEYNOTE-859 establish the importance of Nivolumab, Sintilimab, and Pembrolizumab in the first-line treatment of advanced gastric cancer (GC).[5-7]

Bacterial or viral infections are not only important in triggering the development of certain cancers,[8] but they are also one of the mechanisms that mediate tumor resistance to chemotherapeutic agents.[9] Microorganisms in the body tend to be in a homeostatic state, which can be disrupted under certain circumstances. Antibiotics, while removing pathogenic bacteria from the body, can also destabilize the gut microbiota causing dysbiosis.[10] As the gut microbiota can influence the effectiveness of immune checkpoint inhibitors (ICIs),[11] the use of probiotics appears to restore this disorder and enhance the effects of ICIs.[12] Previous studies have demonstrated that antibiotic use influences the efficacy of immunotherapy.[13,14]

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Antibiotic use seems to be an adverse factor in lung cancer patients treated with ICIs,[15,16] but this finding is controversial in melanoma.[16,17] In GC, however, studies on the relationship between antibiotic use and the efficacy of ICIs are rare. Therefore, the aim of this study was to explore whether the use of antibiotics could change the prognosis of patients with GC who are treated with ICIs.

Patients and methods

GC patients who received ICIs at Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology between February 2019 and February 2022 were recruited for this retrospective study. Antibiotic use within 1 and 3 months prior to the first dose of immunotherapy was obtained from the medical records. It is worth noting that the majority of patients receiving antibiotics in this study were treated prophylactically due to surgery. Therefore, we categorized patients who received antibiotics into 2 groups based on the reason for antibiotic use: prophylactic use and infection (in case of a diagnosed infective disease). However, patients with GC who received antibiotic therapy because of palliative surgery (primary site, metastatic site, etc.) or abbreviated laparotomy were defined as prophylactic antibiotic use. The χ^2 test and Fisher's exact test were performed to compare the differences between the 3 cohorts. Time from immunotherapy initiation to disease progression or death was defined as progression-free survival (PFS) or overall survival (OS). All patients were enrolled in the survival analysis. Survival curves were performed using the Kaplane–Meier method, and the log-rank test was applied to compare the different groups using the Medcalc software. Imaging for the efficacy assessment was reviewed according to the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) criteria.

Results

Patients' characteristics

The study consisted of 252 patients (150 males and 102 females). The median follow-up time and mean age were 21.3 months and 53.7 years, respectively. The pathologic type was adenocarcinoma in 94.8% of patients. The proportions of patients with liver, lung, peritoneal, ovary, supraclavicular lymph nodes, and adrenal gland metastases were 24.2%, 6.7%, 49.2%, 14.7%, 11.9%, and 5.2%, respectively. 63.5% (160/252) of patients were mismatch repair-proficient (pMMR) status and 2.8% (7/252) of patients were mismatch repair-deficient (dMMR) status. The proportions of human epidermal growth factor receptor 2 (HER-2) positive and negative were 5.9% (15/252) and 69.8% (176/252), respectively. The number of cases of first-line, second-line, and third-line immunotherapy were 177, 65, and 10, respectively. Distant metastases were diagnosed in 94.4% of patients. There were only 11 cases of unresectable, locally advanced GC patients in this study. Of all the patients, 3 patients suffered from anastomotic recurrence. Immunotherapy in combination with chemotherapy was the most common treatment option (98.4%, 248/252), with 10 of them receiving trastuzumab concurrently. Only 4 patients (1.6%) were injected with ICIs only (Table 1).

Supplementary Table S1 showed the clinical characteristics of the patients in the 3 cohorts. There were no differences in age, sex, differentiation, and HER-2 status among the 3 groups. The percentage of patients with peritoneal metastases and pMMR was highest among patients with GC who received antibiotics as prophylaxis, at 75.7% and 68.6%, respectively. Not only that, the proportion of patients in this cohort receiving immunotherapy as first-line treatment was 95.7%.

Table 1. Baseline characteristics of the patients.

	N = 252(%)
Age (median)	53.7
Sex	
Male	150 (59.5)
Female	102 (40.5)
Pathology	
Adenocarcinoma	239 (94.8)
Others	13 (5.2)
Sites of metastasis	
Liver	61 (24.2)
Lung	17 (6.7)
Peritoneum	124 (49.2)
Ovary	37 (14.7)
Supraclavicular lymph nodes	30 (11.9)
Adrenal gland	13 (5.2)
Differentiation	
Poor	159 (63.1)
Moderately + Well	9 (3.6)
Unknown	84 (33.3)
MMR status	
pMMR	160 (63.5)
dMMR	7 (2.8)
Unknown	85 (33.7)
Her-2	
Positive	15 (5.9)
Negative	176 (69.8)
Unknown	61 (24.2)
Number of treatment lines	
Fist-line	177 (70.2)
Second-line	65 (25.8)
Third-line	10 (4.0)
Treatment	
ICIs + chemotherapy	238 (94.4)
ICIs + chemotherapy + Trastuzumab	10 (4.0)
ICIs	4 (1.6)
Disease stage	
Metastatic	238 (94.4)
Locally advanced	11 (4.4)
Locally recurrent	3 (1.2)

Abbreviations: dMMR, mismatch repair-deficient; Her-2, human epidermal growth factor receptor 2; ICIs: immune checkpoint inhibitors; pMMR, mismatch repair-proficient.

Patient's antibiotic use

Out of the 252 patients, 38.5% (97/252) had used antibiotics within 1 month before starting immunotherapy. Among these, 72.2% (70/97) had used antibiotics as a preventive measure,

while 27.8% (27/97) had taken them due to an infection. Within 3 months prior to immunotherapy, 48.8% (123/252) of patients had received antibiotics, with 74.8% (92/123) using them for preventive purposes and 25.22% (31/123) due to an infection.

Response to treatment

Patients were categorized into 3 groups according to whether they had used antibiotics within 1 month prior to immunotherapy: none, prophylactic use, and infection. Patients in the infection group had the highest rate (18.5%) of progressive disease (PD). Overall response rate (ORR) was 23.8%, 22.9%, and 22.2%, and disease control rate (DCR) was 91.0%, 94.3%, and 81.5% in the 3 groups, respectively. When time was extended to 3 months, patients in the infected group still had the highest proportion of PD (19.4%), the group without antibiotic exposure had the highest ORR (26.4), and the group with prophylactic antibiotics still had the highest DCR (94.6%) (Supplementary Table S2).

Associations of antibiotic use and outcomes

Figure 1A and E showed that OS was significantly prolonged in patients who received antibiotics within 1 month prior to immunotherapy (20.4 vs 14.7 m, HR, 0.69; 95% CI, 0.49-0.98), while PFS was not significantly improved (P =.1909). However, this survival difference disappeared when the time was extended to 3 months (Figure 1B and F). In a further analysis of 177 patients treated with immunotherapy as first-line treatment, the conclusion that OS was better in patients who used antibiotics within 1 month before immunotherapy also applied (Figure 1C, D, G, and H).

In order to ascertain the relationship between the purpose of antibiotic use and the prognosis of the patients, we divided the patients into 3 groups: none, prophylactic use, and infection. Patients with prophylactic antibiotics within 1 month prior to immunotherapy exhibited significantly longer PFS (12.5 vs 6.3 m; HR, 0.59; 95% CI, 0.32-1.06) and OS (22.6 vs 9.7 m; HR, 0.53; 95% CI, 0.27-1.07) compared with infected patients (Figure 2A and D). The risk of death was reduced by 43% in patients who received prophylactic antibiotics in comparison to those who had not received antibiotics treatment (Figure 2B and E). However, no significant differences in PFS and OS were observed between patients who had not received antibiotics treatment and infected patients who had received antibiotics 1 month prior to immunotherapy (Figure 2C and F).

In GC patients who received immunotherapy as first-line treatment, OS (22.6 vs 14.7 m; HR,0.57; 95% CI, 0.37-0.89) was significantly improved in patients with prophylactic antibiotics compared with those who did not receive antibiotics (Figure 3).

Figure 4A and B demonstrated that palliative surgery was not associated with a survival benefit in patients who received antibiotics prophylactically. In all patients with GC with peritoneal metastases, OS (20.4 vs 13.0 m; HR, 0.50; 95% CI, 0.31-0.82) was significantly prolonged in those who received prophylactic antibiotics (Figure 4C and D).

Prognostic factors associated with OS and PFS

Survival analyses of the total cohort were performed for the following 12 criteria: (1) Age; (2) Sex; (3) Her-2 status; (4) MMR status; (5) Number of treatment lines; (6) Liver metastasis; (7) Lung metastasis; (8) Peritoneum metastasis; (9) Ovary metastasis; (10) Supraclavicular lymph nodes metastasis; (11) Adrenal gland metastasis; and (12) Systemic antibiotics (1 month prior to immunotherapy). Univariate Cox regression showed that 3 variables (MMR status, number of treatment lines, and peritoneum metastasis) were significant prognostic factors for PFS; 2 variables (number of treatment lines and systemic antibiotics) were significant prognostic factors for OS. Multivariate Cox regression using enter regression techniques was performed with these variables that showed that peritoneum metastasis was chosen as the independent factor for PFS and systemic antibiotics was selected as the independent factor for OS (Table 2).

Hematologic indices of patients at baseline

Neutrophil levels were significantly lower in patients with and without prophylactic antibiotics 1 or 3 months before immunotherapy than in infected patients. In contrast, there was no significant difference in leukocytes, lymphocytes, albumin, and neutrophil-to-lymphocyte ratio (NLR) at baseline among the 3 groups of patients (Figure 5).

Discussion

Previous studies have shown that patients with a history of antibiotic use prior to immunotherapy have a worse prognosis.[18] In addition, the use of antibiotics prior to immunotherapy seemed to be able to increase the risk of adverse immune events in patients.[19] However, some researchers have pointed out that antibiotic use does not increase the risk of death in patients who have received immunotherapy.[20] Even Muntaha Naeem et al. in an observational study stated that antibiotic use is a favorable protective factor for hepatocellular carcinoma patients receiving ICIs.[21] A study indicates that prophylactic antibiotic use rather than antibiotic use at the time of infection can increase the risk of death in immunotherapy patients.[22] Additionally, the sequence in which antibiotics and ICIs are administered seems to influence the survival outcome of patients.[23] Thus, the effect of antibiotics on the efficacy of ICIs is extremely complex.

Currently, there is a paucity of research on the effect of antibiotics on immunotherapy for GC. The study by Chang Gon Kim et al. pointed out that antibiotics used prior to immunotherapy can increase the risk of disease progression as well as death in patients with GC by reducing the diversity of gut microbes.[24] Nevertheless, results of a retrospective study showing the use of antibiotics do not apparently affect the efficacy of immunotherapy in patients with esophago GC.[25] But the above-mentioned 2 studies did not provide a reason for the patients' use of antibiotics. Interestingly, our results, which have shown that antibiotic use is a protective factor for GC patients receiving immunotherapy, are diametrically opposed to previous studies. However, this protective effect is limited to prophylactic use.

The relationship between palliative surgery and the prognosis of patients with GC is controversial. To determine whether this survival benefit was correlated with surgery, we categorized patients who received prophylactic antibiotic therapy into 2 groups according to the purpose of the operation: palliative surgery and abbreviated laparotomy. The results of this study indicated that the prolongation of patients' OS was not attributable to palliative surgery.

Certain patients with advanced GC often need to be subjected to surgery due to bleeding, perforation, obstruction,

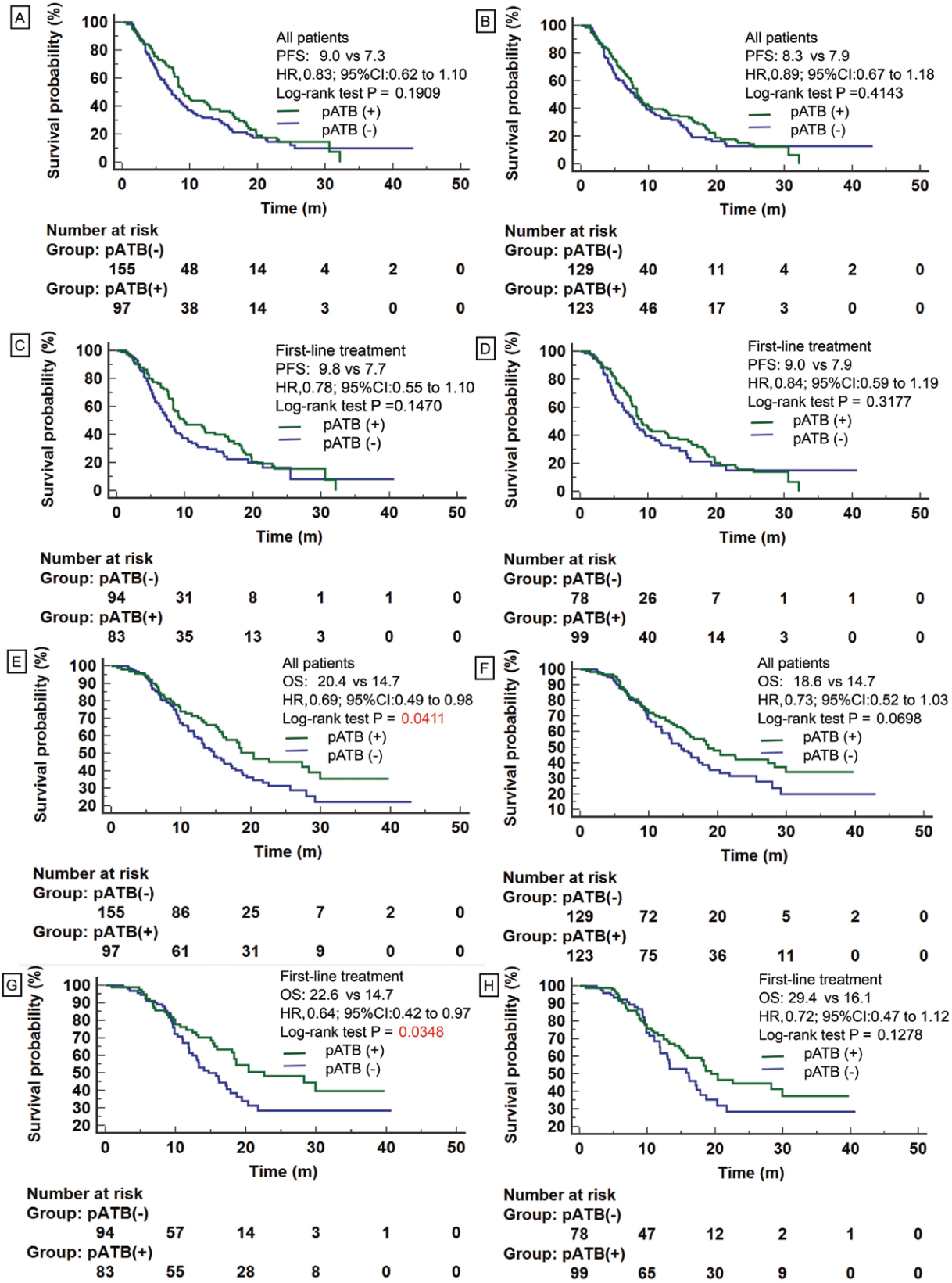

Figure 1. Kaplan–Meier analysis of overall survival and progression-free survival for patients who had been treated with immunotherapy with or without antibiotics within 1 month (All patients: A and E; Immunotherapy as first-line treatment: C and G) or 3 months (All patients: B and F; Immunotherapy as first-line treatment: D and H) prior to the start of immunotherapy. pATB: prior antibiotic treatment.

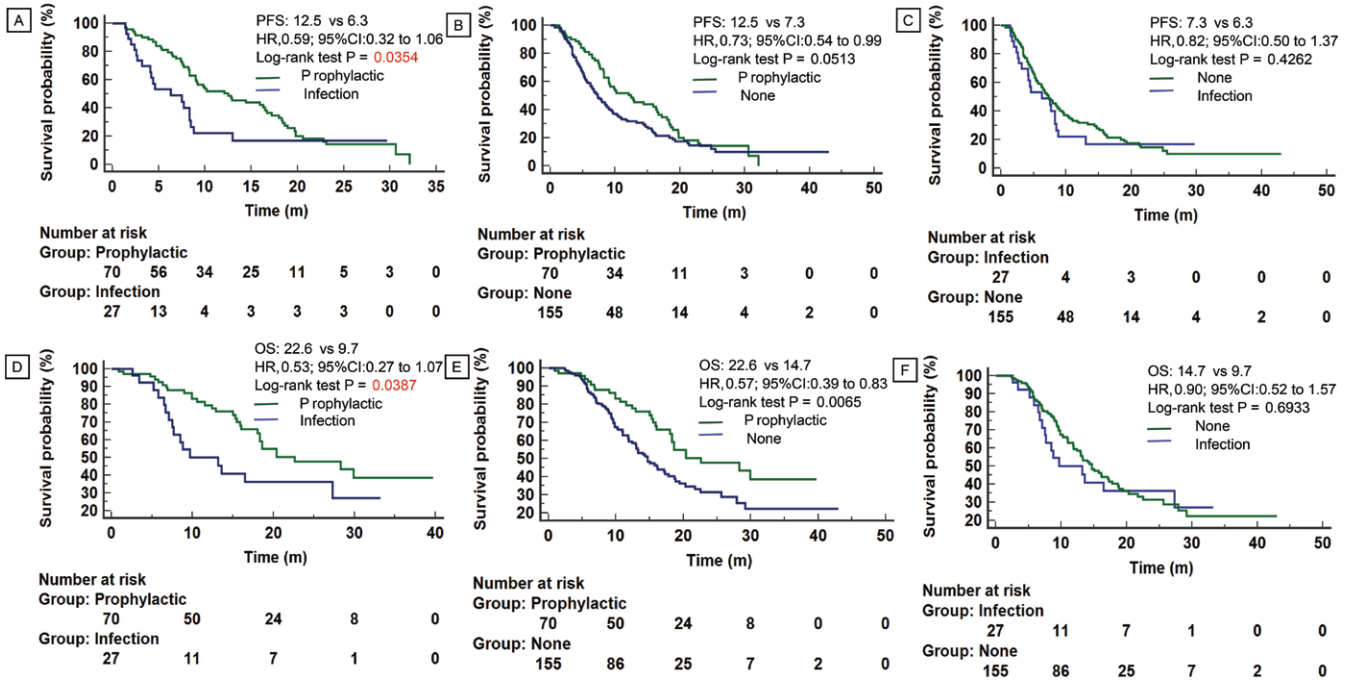

Figure 2. Kaplan–Meier analysis of overall survival and progression-free survival for patients who had been treated with antibiotics or without antibiotics (Prophylactic vs Infection: A and D; Prophylactic vs None: B and E; None vs Infection: C and F) within 1 month prior to start of immunotherapy in all patients.

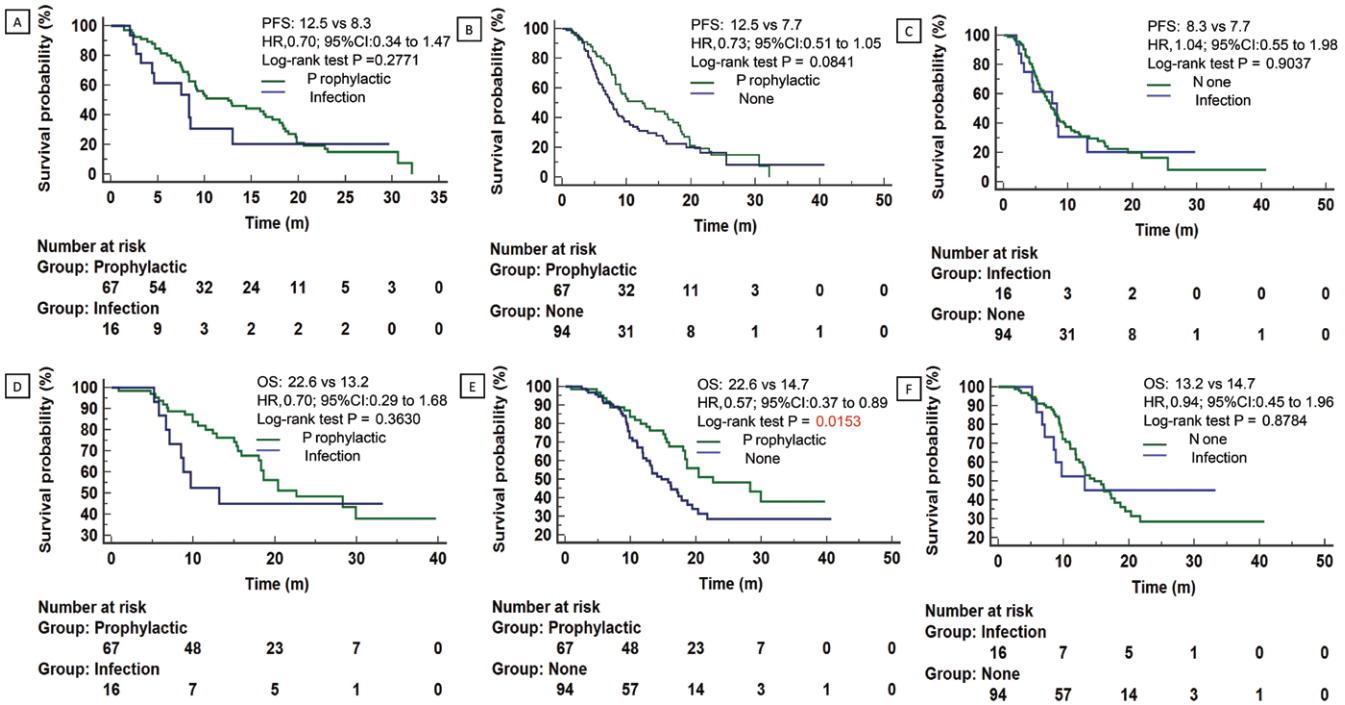

Figure 3. Kaplan–Meier analysis of overall survival and progression-free survival for patients who had been treated with antibiotics or without antibiotics (Prophylactic vs Infection: A and D; Prophylactic vs None: B and E; None vs Infection: C and F) within 1 month prior to the start of immunotherapy in patients with immunotherapy as first-line treatment.

etc.[26] Peritoneal metastasis is one of the common sites of metastasis in patients with GC, and previous studies have confirmed that the sensitivity of computed tomographic (CT) for peritoneal metastasis is only 28.3%-50.9%.[27] Peritoneal metastases were identified at the time of surgery in 25% of GC patients even if their preoperative CT showed no peritoneal metastases.[28] Therefore, prophylactic use of antibiotics before immunotherapy is unavoidable in some GC patients.

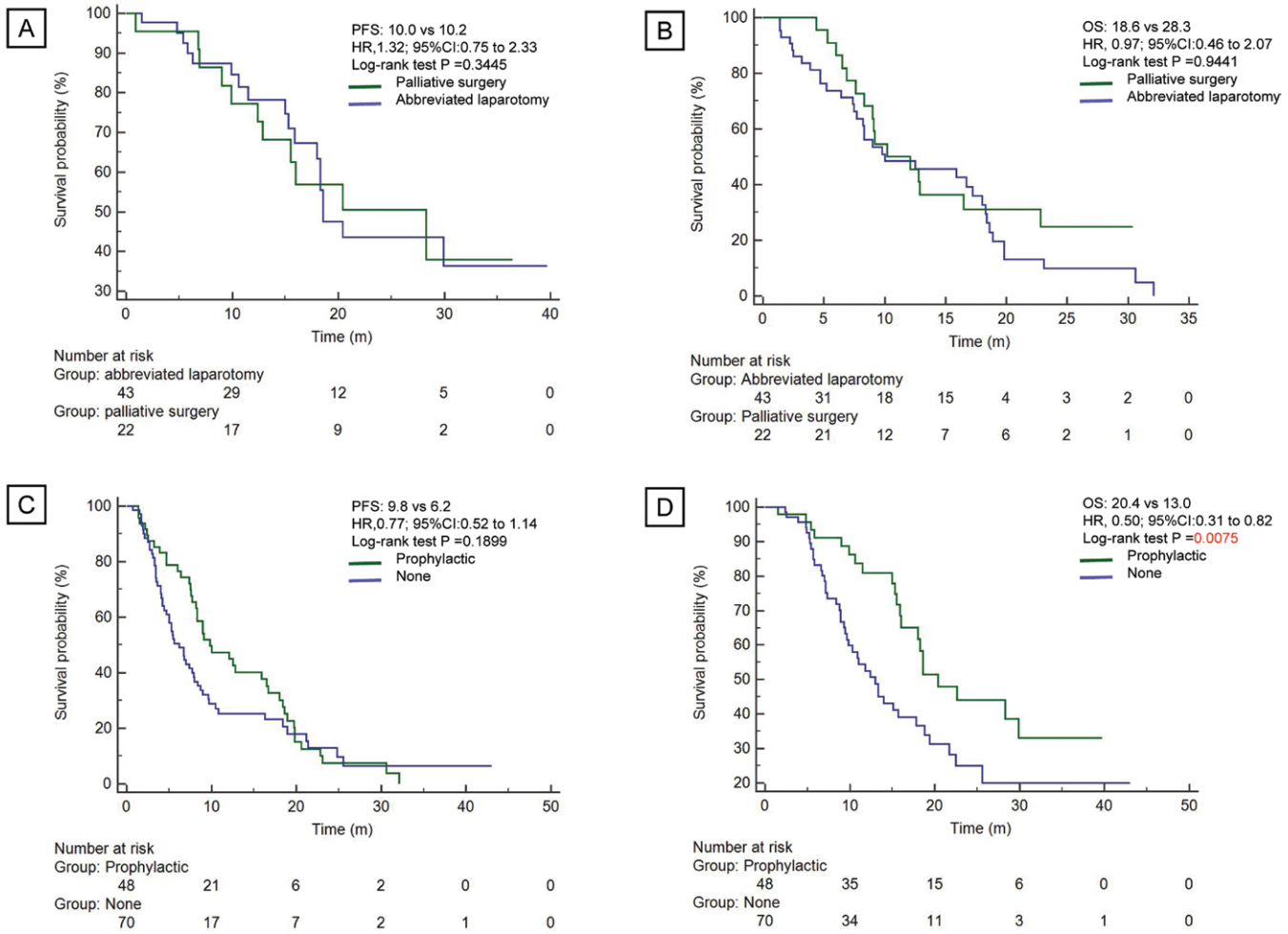

Figure 4. Kaplan–Meier analysis of overall survival (OS) and progression-free survival (PFS) for patients who had been treated with antibiotics due to palliative surgery or abbreviated laparotomy within 1 month prior to the start of immunotherapy (A and B). Kaplan–Meier analysis of OS and PFS for patients with peritoneum metastasis (C and D).

Interestingly, the results of this study suggested that peritoneal metastasis was an independent predictor of a better prognosis for patients. We unexpectedly observed that prophylactic antibiotic use improved patients' OS from 13.0 to 20.4 months when analyzing patients with peritoneal metastases. It is reconfirmed that prophylactic use of antibiotics may be associated with improved survival in patients with GC.

The effect of antibiotics on the diversity and composition of gut microorganisms is thought to be one of the important mechanisms by which antibiotics affect the efficacy of immunotherapy. The use of antibiotics is often due to the presence of bacterial infections. The study by Qiang Cao et al. noted that lung cancer patients with bacterial infections had a better response to immunotherapy,[29] but whether this benefit was due to the use of antibiotics is unknown. In our study, antibiotic use in infected patients did not increase or decrease their risk of death. However, one of the limitations of this study is that the sample size of infected patients was too small; therefore, a larger sample size was needed for further validation. Furthermore, there are still some limitations in this study. It is well known that *Helicobacter pylori* (HP) infection, dMMR, or PD-L1 scores are closely associated with the efficacy of immunotherapy. Unfortunately, however, only 10 patients were tested for HP (data not shown), 7 patients with dMMR status, and only 16 patients with available PD-L1 scores (data not shown) in this study. Therefore, further subgroup analyses could not be performed. A larger sample size study should be designed to analyze whether the type of antibiotic and the mode of antibiotic treatment (oral, intramuscular injection, intravenous, etc.) can make an influence in the patient's prognosis.

Neutrophils are one of the most common and important immune cells. Neutrophils with plasticity have a dual role of tumor suppression and tumor promotion,[30,31] which may be due to the different origin of progenitor cells. High levels of pretreatment NLR predict a worse prognosis for patients receiving immunotherapy.[32] However, our findings revealed that patients prophylactically using antibiotics had lower neutrophil levels rather than NLR at baseline compared with infected patients. A retrospective study revealed that low neutrophils rather than NLR was associated with higher complete pathological response rate in patients with locally advanced rectal cancer receiving short course radiotherapy followed by chemotherapy and immunotherapy.[33] Antibiotics are more commonly thought to influence immunotherapy efficacy by altering gut microbes. Whether antibiotics influence

Table 2. Univariate and multivariate Cox model analyses of clinicopathological characteristics for overall survival and progression-free survival (all patients).

	PFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	1.001 (0.990–1.013)	.828	1.007 (0.994–1.021)	.296	1.003 (0.989–1.017)	.661	1.007 (0.991–1.024)	.403
Sex		.148		.619		.452		.123
Male	1		1		1		1	
Female	0.809 (0.608–1.078)		0.916 (0.649–1.293)		1.145 (0.804–1.630)		1.404 (0.912–2.161)	
Her-2		.736		.742		.812		.998
Negative	1		1		1		1	
Positive	0.815 (0.440–1.509)	.515	0.773 (0.400–1.491)	.442	0.892 (0.433–1.839)	.757	0.991 (0.459–2.140)	.982
Unknown	1.058 (0.761–1.471)	.736	0.943 (0.609–1.460)	.793	1.115 (0.738–1.686)	.604	1.015 (0.604–1.705)	.956
MMR status		.128		.279		.364		.400
pMMR	1		1		1		1	
dMMR	0.245 (0.061–0.994)	.049	0.310 (0.073–1.316)	.112	0.245 (0.034–1.763)	.163	0.267 (0.035–2.004)	.199
Unknown	1.053 (0.778–1.424)	.739	1028 (0.685–1.542)	.895	1.034 (0.715–1.496)	.858	0.897 (0.563–1.430)	.648
Number of treatment lines		.104		.455		.029		.171
Fist-line	1		1		1		1	
Second-line	1.418 (1.028–1.956)	.034	1.171 (0.807–1.697)	.406	1.668 (1.142–2.438)	.008	1.386 (0.906–2.120)	.132
Third-line	1.070 (0.499–2.294)	.863	0.721 (0.322–1.613)	.426	1.027 (0.417–2.534)	.953	0.660 (0.254–1.714)	.394
Liver metastasis		.668		.921		.647		.230
Yes	1		1		1		1	
No	0.927 (0.656–1.310)		0.979 (0.645–1.487)		0.908 (0.601–1.372)		0.740 (0.453–1.210)	
Lung metastasis		.679		.391		.730		.718
Yes	1		1		1		1	
No	1.122 (0.650–1.935)		1.304 (0.711–2.390)		1.127 (0.572–2.222)		1.145 (0.548–2.396)	
Peritoneum metastasis		.050		.025		.296		.112
Yes	1		1		1		1	
No	1.331 (1.000–1.771)		1.526 (1.055–2.207)		1.202 (0.852–1.696)		1.425 (0.921–2.205)	
Ovary metastasis		.110		.399		.605		.376
Yes	1		1		1		1	
No	1.356 (0.934–1.968)		1.219 (0.769–1.933)		1.124 (0.721–1.752)		1.295 (0.731–2.296)	
Supraclavicular lymph nodes metastasis		.344		.277		.189		.204
Yes	1		1		1		1	
No	1.240 (0.794–1.937)		1.330 (0.795–2.226)		1.408 (0.845–2.349)		1.475 (0.810–2.684)	
Adrenal gland metastasis		.523		.800		.888		.886
Yes	1		1		1		1	
No	0.794 (0.391–1.613)		0.898 (0.391–2.061)		1.061 (0.467–2.408)		1.071 (0.420–2.734)	

Table 2. Continued

	PFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Systemic antibiotics (1 month)		.086		.073		.023		.018
Prophylaxis	1		1		1		1	
Infection	1.644 (0.982–2.751)	.059	1.948 (1.066–3.561)	.030	1.906 (1.038–3.500)	.037	2.462 (1.220–4.968)	.012
None	1.357 (0.982–1.874)	.064	1.374 (0.948–1.990)	.093	1.746 (1.147–2.658)	.009	1.817 (1.132–2.918)	.013

Abbreviations: OS, overall survival; PFS, progression-free survival.

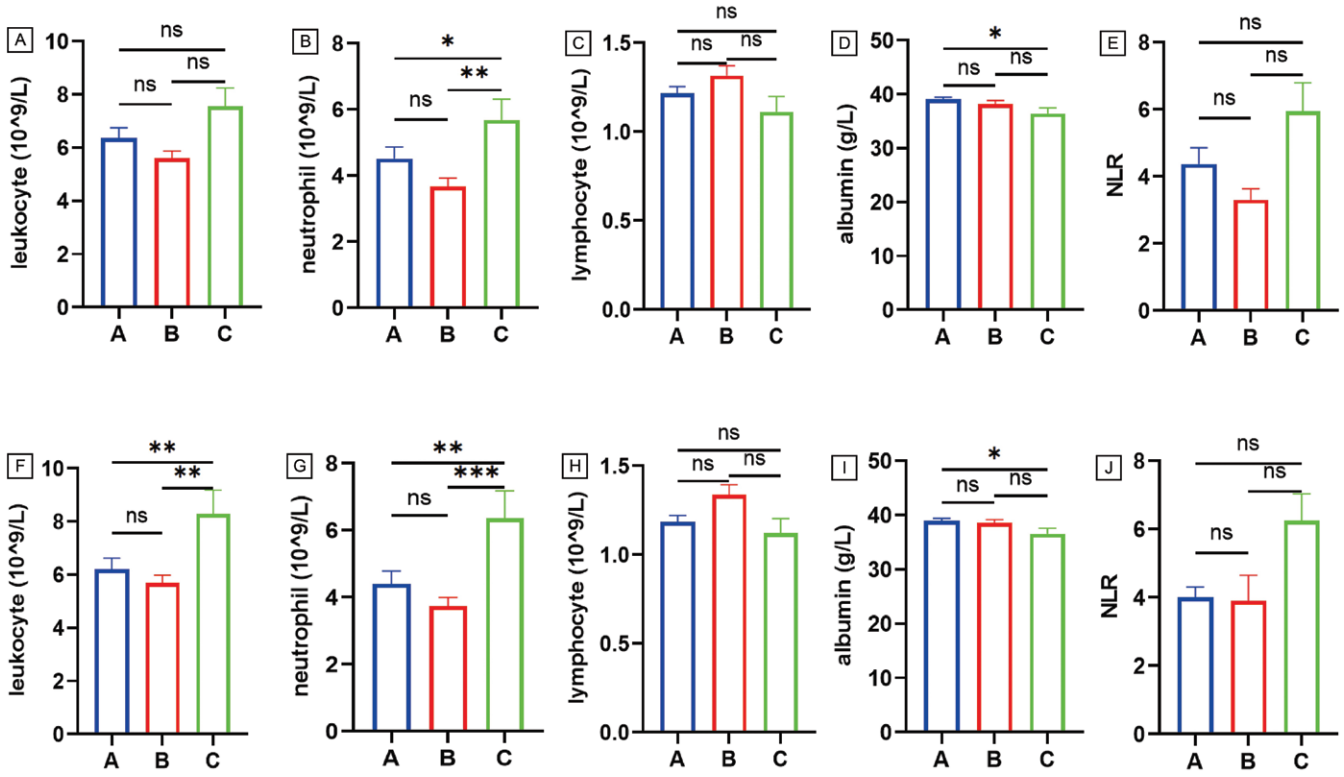

Figure 5. Baseline levels of leukocytes, neutrophils, lymphocytes, albumin, and NLR in patients receiving immunotherapy with or without antibiotics within 1 month (A-E) or 3 months (F-J) prior to the start of immunotherapy. arm A: none; arm B: prophylactic; arm C: infection.

the efficacy of immunotherapy by modulating neutrophil differentiation is worth further exploration.

Conclusion

We confirmed the association between prophylactic use of antibiotics and better clinical outcomes with immunotherapy. Therefore, there is no necessity to delay the use of ICIs in this group of patients. The treatment of antibiotics due to infection did not seem to increase the risk of death in patients, but further validation in large cohorts is imperative.

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Author contributions

Fangyuan Zhang (Data curation, Writing—original draft, Conceptualization), Zixuan Ding (Writing—original draft, Data curation), Yongping Lian (Writing—original draft, Methodology), Xiao Yang (Writing—original draft, Resources), Pengbo Hu (Writing—original draft, Software), Yongqing Liu (Writing—original draft, Software), Liang Xu (Writing—original draft, Validation), Zhou Li (Writing—

original draft, Validation), and Hong Qiu (Conceptualization, Writing—review & editing)

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Conflict of Interest

The authors declare that they have no conflict of interest.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary material

Supplementary material is available at *The Oncologist* online.

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