Annals of Gastroenterology (2025) **38,** 262-269

Helicobacter pylori infection negatively affects response of gastric cancer to immunotherapy

Malek Shatila[a], Gabriel Sperling[b], Antonio Pizuorno Machado[c], Muhammad Vohra[c], Elliot Baerman[d], Enrico N. De Toni[e], Helga-Paula Török[e], Dan Zhao[f], Yan Zhou[g], Mehnaz A. Shafi[a], Anusha Shirwaikar Thomas[a], Mazen Alasadi[a], Yinghong Wang[a]

The University of Texas MD Anderson Cancer Center, Houston, TX, USA; Baylor College of Medicine, Houston, TX, USA; University Hospital, Ludwig-Maximilians-University Munich, Munich, Germany

Abstract

Background *Helicobacter pylori* (*H. pylori*) is a known risk factor for gastric cancer, possibly via the PD-1/L1 pathway, and this infection may reduce the efficacy of immune checkpoint inhibitors (ICIs). This study explored the effects of *H. pylori* infection status on survival outcomes in patients with gastric cancer.

Methods This single-center, retrospective study included patients with gastric adenocarcinoma between June 1985 and August 2022. Patients with different histological subtypes were excluded. Primary variables of interest included *H. pylori* infection status and treatment with ICIs. Other clinical information included demographics, cancer histology, the presence of other cancers, and vital status.

Results A total of 2930 patients were included, of whom 206 (7.0%) received ICIs, 196 (6.7%) had prior *H. pylori* infection, and 1037 (35.4%) had a diffuse subtype. Diffuse cancer subtypes were associated with better survival (P<0.05) at 3 and 5 years compared to intestinal-type adenocarcinomas. Diffuse cancers demonstrated better survival outcomes than intestinal cancers at 10 years, but only among *H. pylori*-positive patients (P=0.013). *H. pylori* positivity was associated with worse survival at 3 years (P=0.041) among patients taking ICIs, but not in those not receiving ICIs (P=0.325).

Conclusions These findings suggest *H. pylori* infection may be an obstacle to successful immunotherapy, and may interact with cancer subtypes to differentially impact survival. Future studies are needed to validate the potential prognostic value of *H. pylori* positivity in gastric cancer.

Keywords *Helicobacter pylori*, immunotherapy, gastric cancer

Ann Gastroenterol 2025; 38 (3): 262-269

Conflict of Interest: None

Correspondence to: Dr. Yinghong Wang, MD, PhD, Department of Gastroenterology, Hepatology, and Nutrition, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Unit 1466, Houston, TX 77030, e-mail: ywang59@mdanderson.org

Received 4 November 2024; accepted 7 April 2025; published online 28 April 2025

DOI: https://doi.org/10.20524/aog.2025.0966

Introduction

Gastric cancer is a significant cause of morbidity and mortality globally, ranking as the fifth most common cancer and the third most common cause of cancer death worldwide [1]. Some regions, namely East Asia, Eastern Europe and South America, have been identified as areas with a high prevalence of gastric cancer, and the incidence of such cancer is twice as high in men than in women [2]. It has been well documented that *Helicobacter pylori* (*H. pylori*) infection is the strongest risk factor for gastric cancer, with the World Health Organization classifying it as a class I (definite) carcinogen [3]. Infections are estimated to account for about two thirds of newly diagnosed gastric cancers [4], and *H. pylori*

eradication reduces the incidence of gastric cancer by more than 40% [5]. Additional notable risk factors for gastric cancer include older age, low socioeconomic status, dietary factors, smoking cigarettes, familial predisposition, previous gastric surgery, and pernicious anemia. The clinical presentation can vary widely, and largely depends on the aforementioned risk factors, with up to 68% of infections being asymptomatic [6]. The most common symptoms include epigastric abdominal pain, dyspepsia, bloating, nausea or vomiting, lack of appetite, dark or tar-colored stools and anemia [7]. Overall, outcomes for individuals with stomach cancer are quite poor. Worldwide, the 5-year relative survival rate is 20-30%, excluding that for Japan (69%) and Korea (67%) [8].

The Lauren criteria classify gastric cancer into 2 main types: diffuse and intestinal [9]. The diffuse subtype refers to mucin-producing adenocarcinomas, including signet-ring-cell gastric cancer and mucinous gastric cancers. These subtypes are known to demonstrate more aggressive growth and invasiveness and to have a poorer prognosis compared to their intestinal-type counterparts [10]. While *H. pylori* infection status does not appear to have a significant effect on the prevalence of the different subtypes, diffuse gastric cancers have been shown to have a greater frequency of PD-L1 expression, which may have important implications for the efficacy of treatment for gastric adenocarcinomas secondary to *H. pylori* infection [11].

There are various treatment options for gastric cancer, with a combined modality of medical and surgical management being the most common treatment approach. More recently, immune checkpoint inhibitors (ICIs) became a standard treatment for chemorefractory gastric cancer. Results from multiple trials show that patients with chemorefractory gastric cancer taking nivolumab and pembrolizumab, both PD-1 antibodies, have similar or better overall survival outcomes compared to such patients taking a placebo [12,13]. Additional data support the use of several anti–PD-1 drugs in combination with standard chemotherapy as a first-line treatment, although further investigation is ongoing [14,15].

Interestingly, *H. pylori* virulence factors, such as Cytotoxic antigen A (CagA), induce PD-1 expression, facilitating *H. pylori* infection and eventual tumorigenesis [16]. Several animal studies have shown the importance of the PD-1 pathway in the *H. pylori* inflammatory process through this same mechanism [17]. Therefore, *H. pylori* infection should theoretically hinder the efficacy of ICIs used for cancer treatment, particularly that of anti–PD-1/L1 agents, leading to worse patient outcomes. This conclusion is supported by a recently published European study that found that: (a) *H. pylori* infection partially blocks the activity of ICIs in murine models; and (b) *H. pylori* seropositivity is correlated with lower effectiveness of anti–PD-1 immunotherapy in patients with lung cancer [18]. Both of these findings illustrate the importance of stomach microbiota in the immunotherapy response. However, there have been minimal studies to date of this phenomenon in human populations. To fill this knowledge gap, we aimed to explore the effect of *H. pylori* infection status on survival in patients with gastric cancer.

[a]Department of Gastroenterology, Hepatology, and Nutrition, The University of Texas MD Anderson Cancer Center, Houston, TX, USA (Malek Shatila, Mehnaz A. Shafi, Anusha Shirwaikar Thomas, Mazen Alasadi, Yinghong Wang); [b]Department of Internal Medicine, The University of Texas Medical Branch, Galveston, TX, USA (Gabriel Sperling); [c]Department of Internal Medicine, The University of Texas Health Science Center, Houston, TX, USA (Antonio Pizuorno Machado, Muhammad Vohra); [d]Department of Internal Medicine, Baylor College of Medicine, Houston, TX, USA (Elliot Baerman); [e]Department of Medicine II, University Hospital, Ludwig-Maximilians-University Munich, Munich, Germany (Enrico N. De Toni, Helga-Paula Török); [f]Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA (Dan Zhao); [g]Department of Hospital Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA (Yan Zhou)

Patients and methods

Patient selection and data collection

We conducted a retrospective, single-center study of all patients diagnosed with gastric adenocarcinoma between June 1, 1985, and August 31, 2022. Patients were included in this study if they (1) were 18 years or older and (2) had a diagnosis of gastric adenocarcinoma. Patients diagnosed with a different cancer subtype (lymphoma, neuroendocrine tumors, metastases, etc.) were excluded. We extracted oncological data and data on patient demographics, *H. pylori* infection status, cancer treatments and outcomes from the patients' electronic health records. Primary variables of interest included *H. pylori* infection status and history of treatment with ICIs. For this reason, we created subgroups of patients based on their *H. pylori* status at any timepoint, whether or not they received an ICI for their gastric cancer, and the gastric cancer subtype (diffuse or intestinal).

Cancer subtype

Cancer subtype was determined based on pathology reports from tissue biopsies obtained from patients. Patients with histological reports describing mucinous adenocarcinomas, mucin-producing adenocarcinomas, signet-ring cell carcinoma, and linitis plastica were grouped together as diffuse-type adenocarcinomas. Otherwise, patients were considered to have intestinal-type adenocarcinomas when their histology results reported adenocarcinoma without any of the aforementioned descriptors.

H. pylori status

H. pylori infection status was determined by the presence of a positive urea breath test result, stool antigen test result, serological marker test result, endoscopic biopsy result, or documentation of an ICD code for *H. pylori* infection. If no such tests had been recorded in a patient's chart, we considered the patient to be *H. pylori*-naïve, and if the results of such tests were negative, the patient was considered to be *H. pylori*-negative.

Patient charts were reviewed to confirm *H. pylori* treatment and eradication. If this information was not documented, the patient was considered not to have undergone treatment or eradication.

Statistical analysis

Statistical analyses were conducted using SPSS version 26.0. Continuous variables were described by their median and interquartile range. Categorical variables were described by their frequency and percentage of the total. The Fisher exact test was used to compare differences between categorical variables. Finally, multivariate Cox hazard survival analysis was used to compare overall survival from the date of gastric cancer diagnosis between different groups.

Results

Patient information

The patient selection flowchart can be found in Fig. 1. A total of 2930 patients were included in the final analysis. Our sample was predominantly male (65.6%) and white (64.2%), with a median age of 64 years (interquartile range 54-73). All patients had gastric cancer, with most having intestinal-type adenocarcinoma on histology (1893 patients; 64.6%). The remaining 1037 patients (35.4%) had diffuse-type carcinomas. Only 34 patients (1.2%) had other cancers, either concurrent with or after the onset of gastric cancer. One hundred ninety-six patients (6.7%) had a prior diagnosis of *H. pylori*, and 206 patients (7.0%) received ICIs; of these patients, most received some form of PD-1/L1 inhibition, with 86.4% receiving anti–PD-1/L1 monotherapy, 11.7% receiving combination immunotherapy, and only 1.9% (n=4) receiving anti–CTLA-4 monotherapy. Finally, 923 patients (31.5%) were deceased at last follow up, with a median follow-up duration of 1.4 (0.7-3.0) years. Patients' basic oncologic characteristics can be found in Table 1.

Supplementary Table 1 shows a comparison of baseline characteristics among *H. pylori*-positive and *H. pylori*-negative patients. We found that *H. pylori*-positive patients were more likely to be male (P=0.005) and Asian (P<0.001), and were a median of 3 years younger (P=0.015). They were also found to have a higher all-cause mortality rate (P=0.011), with a longer median follow-up duration (P=0.003). There was no significant difference in cancer stage between the 2 groups (P=0.464).

Associations among cancer subtype and *H. pylori* infection or ICI use

The results of the chi square test for associations among cancer subtype, *H. pylori* infection, and ICI use can be found in Supplementary Tables 1 and 2. Diffuse-type cancer was more frequently associated with *H. pylori* infection, at a rate of 8.2% compared to that of 5.9% for patients with intestinal-type adenocarcinoma (P=0.017). Patients with intestinal-type gastric adenocarcinomas more frequently underwent ICI treatment (8.9% vs. 3.6% in the diffuse subgroup, P<0.001).

Survival analysis

The univariate survival analysis can be found in Supplementary Table 3. *H. pylori* eradication was not associated with survival on univariate analysis. The multivariate Cox hazard analysis for survival at 5 and 10 years showed that

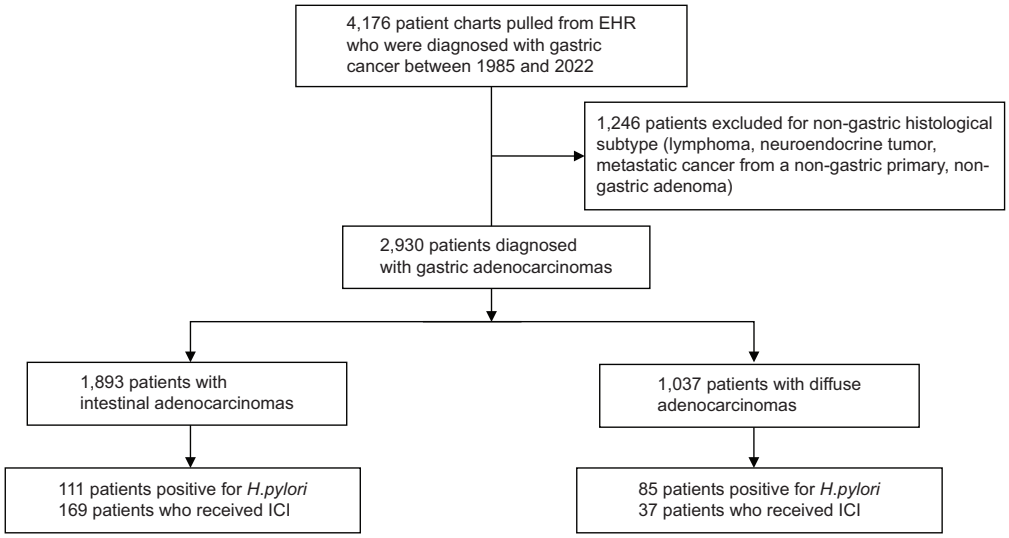

Figure 1 Patient selection flow chart
EHR, electronic health record; ICI, immune checkpoint inhibitors; H. pylori, Helicobacter pylori

Table 1 Demographic characteristics of patients with gastric adenocarcinoma, n=2930

Characteristic	No. (%)
Age, years, median (IQR)	63.8 (53.6-72.9)
Male sex	1922 (65.6%)
Race	
White	1882 (64.2%)
Asian	233 (7.9%)
Gastric cancer subtype	
Diffuse adenocarcinoma	1037 (35.4%)
Intestinal adenocarcinoma	1893 (64.6%)
Presence of other cancers	34 (1.2%)
HP infection	196 (6.7%)
Received ICI	206 (7.0%)
ICI type – n=206	
Anti-PD-1/L1 inhibitor	178 (86.4%)
Anti-CTLA-4 inhibitor	4 (1.9%)
Combination therapy	24 (11.7%)
All-cause mortality	923 (31.5%)
Duration of follow up, years, median (IQR)	1.4 (0.7-3.0)

IQR, interquartile range; HP, Helicobacter pylori; ICI, immune checkpoint inhibitor

diffuse subtype (odds ratio [OR] 0.8, 95% confidence interval [CI] 0.7-0.9), age (OR 0.9, 95%CI 0.9-0.9) and ICI use (OR 2.1, 95%CI 1.7-2.6) were associated with survival at 5 years, whereas only age (OR 0.9, 95%CI 0.9-0.9) and ICI use (OR 1.7, 95%CI 1.4-2.1) were associated with survival at 10 years (Table 2). However, an interaction effect was noted between cancer subtype and *H. pylori* infection status, and between cancer subtype and ICI use at 10 years. We conducted a subgroup analysis (Supplementary Table 4) and found that the diffuse adenocarcinoma subtype was significantly associated with better survival (OR 0.5, 95%CI 0.2-0.8; P=0.013) at 10 years, but only among *H. pylori*-patients (Fig. 2A). Diffuse cancer subtypes had no impact on survival at 10 years among patients without *H. pylori* (OR 0.9, 95%CI 0.8-1.0; P=0.120; Fig. 2B). Similar analyses were conducted for 1- and 3-year survival, but no significant associations were found.

To explore the influence of *H. pylori* infection on immunotherapy efficacy, we conducted a similar survival analysis looking only at patients who received ICIs (Table 3). We found that *H. pylori* infection was significantly associated with worse survival (OR 2.0, 95%CI 1.0-4.0) at 3 years (P=0.041), as shown in the survival curve in Fig. 3. This association was not significant among patients who did not receive ICIs. We did not find a similar trend for 5-year survival (OR 1.5, 95%CI 0.8-2.6; P=0.224 for *H. pylori* infection among patients receiving ICI).

Discussion

In this study, we investigated the survival of patients with gastric cancer; more specifically, the relationship between *H. pylori* and the efficacy of immunotherapy. Based on previous studies, we hypothesized that infection with *H. pylori* reduces the efficacy of certain classes of ICI by inducing PD-1/L1 expression, directly counteracting their effect. Our results show that previous or active *H. pylori* positivity was significantly associated with worse 3-year survival among patients with gastric cancer who underwent ICI therapy, but was not associated with survival among patients who did not undergo such therapy, suggesting a selective detrimental impact on the immunotherapy's effect. Moreover, we found that there may be an interaction between *H. pylori* positivity and cancer subtype, with intestinal adenocarcinomas having significantly worse survival at 10 years compared to diffuse-type tumors. Considering that a significantly higher number of patients with intestinal-type tumors received ICI, this finding further reflects the potentially deleterious influence *H. pylori* positivity has on the success of immunotherapy.

There is an established association between *H. pylori* infection and gastric cancer, which was the rationale for studying this population. Infection with *H. pylori* is a significant risk factor for the development of both diffuse and intestinal gastric cancers, with *H. pylori* implicated in an estimated 75-89% of gastric cancer cases [19,20]. The main mechanisms of gastric carcinogenesis by this pathogen involve chronic inflammation, disruption of mitogenic signaling pathways, and degradation or mutation of proto-oncogenes [20]. The eponymous Correa pathway describes gastric carcinogenesis as a multistep cascade that begins with chronic gastrointestinal inflammation and progresses to atrophic gastritis with intestinal metaplasia, followed by cellular dysplasia that eventually develops into gastric adenocarcinomas [21]. *H. pylori* virulence factors play a critical role in this inflammatory cascade, but their contribution to tumorigenesis is diverse. The most well-studied *H. pylori* virulence factor, CagA, is a notorious oncoprotein that is present in up to 60% of *H. pylori* strains and has been directly implicated in gastric carcinogenesis [22]. Once injected into the gastric epithelial cell, CagA becomes phosphorylated and interacts with an SRC homology 2 domain-containing tyrosine phosphatase (SHP-2), which is known to regulate cell differentiation and growth-related pathways to promote aberrant mitotic patterns [23-25]. In addition, CagA impairs the functioning of the TP53 tumor suppressor gene by physically interacting with its protein product, counteracting its action by activating ubiquitin ligases that degrade the proto-oncogene, and by facilitating the development of spontaneous loss-of-function mutations of the *TP53* gene, among others [22,26,27].

The risk of diffuse-type adenocarcinomas is typically associated with genetic factors, unlike the intestinal subtype, which has traditionally been attributed to environmental factors [28,29]. Thus, it been suggested that CagA promotes intestinal metaplasia by inducing the expression of intestine-specific caudal-related homeobox transcription factors [30]. While *H. pylori* has been implicated in both gastric cancer subtypes, our study found a significant association between *H. pylori* and diffuse-type adenocarcinomas. This was

Table 2 Multivariate Cox Hazard analysis for 5- and 10-year survival

Variable	5-year survival		10-year survival	
	Hazard ratio	P-value	Hazard ratio	P-value
HP vs. no HP	1.1 (0.7-1.7)	0.618	1.4 (1.0-1.9)	0.068
Diffuse adenocarcinoma vs. intestinal adenocarcinoma	0.8 (0.6-0.9)	0.014*	0.9 (0.8-1.1)	0.360
Receiving ICI vs. no ICI	1.9 (1.4-2.5)	<0.001*	2.0 (1.6-2.6)	<0.001*
Age	0.9 (0.9-0.9)	<0.001*	0.9 (0.9-0.9)	<0.001*
Race: African American vs. Asian	0.7 (0.5-1.0)	0.072	0.8 (0.6-1.1)	0.177
Race: White vs. Asian	1.1 (0.9-1.3)	0.469	1.1 (0.9-1.3)	0.209
Presence of other non-GI cancers	1.5 (0.8-2.6)	0.174	1.4 (0.8-2.4)	0.224
Cancer subtype† × HP status	0.6 (0.3-1.3)	0.253	0.6 (0.3-0.9)	0.044*
Cancer subtype† × ICI treatment	0.6 (0.3-1.4)	0.254	0.4 (0.2-0.9)	0.024*
HP status × ICI treatment	1.3 (0.6-2.8)	0.523	0.9 (0.5-2.0)	0.962
Cancer subtype × HP status × ICI treatment	1.5 (0.2-10.0)	0.655	2.8 (0.5-17.2)	0.264

*Significant at the P<0.05 level

†Diffuse gastric adenocarcinoma or intestinal gastric adenocarcinoma

HP, Helicobacter pylori; ICI, immune checkpoint inhibitors; GI, gastrointestinal

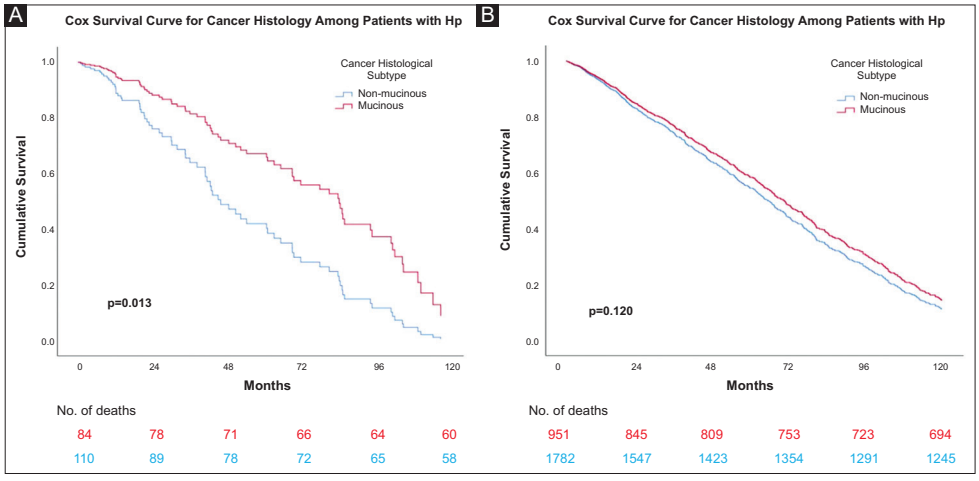

Figure 2 (A and B) Cox survival curves for 10-year survival based on cancer subtype among patients with (left) and without (right) *Helicobacter pylori* (Hp)

probably due to the declining prevalence of *H. pylori* in the United States, where this study was conducted [31]. Because intestinal-type adenocarcinomas are more closely tied to environmental factors, the gradual elimination of *H. pylori* in the United States means that patients presenting with this gastric cancer subtype are likely to have acquired it from environmental factors, such as obesity, smoking, and a diet high in salt and nitrosamine-containing foods [32,33]. That is, patients with *H. pylori*-related gastric cancer are more likely to have the diffuse subtype, or the subtype associated with genetic factors.

Current treatment guidelines for unresectable gastric adenocarcinoma are not dependent on the subtypes, and call for the use of platinum-based agents alongside fluoropyrimidines as a first-line therapy, with trastuzumab for HER2-positive gastric adenocarcinoma [34]. There is, however, value in exploring the impact of cancer subtype on treatment efficacy. One study by Stiekema *et al* suggests that diffuse-type tumors may be adverse prognostic factors for survival following gastric resection [35]. However, diffuse adenocarcinomas may be more responsive to systemic treatments [36-39]. Our study found that diffuse adenocarcinomas were associated with better survival in our cohort, which contradicts the established research showing a poorer prognosis among patients with this subtype [10]. However, a potentially higher efficacy of systemic therapy for this subtype of gastric cancer may explain this finding.

Immunotherapy with ICIs is a relatively new addition to the treatment armamentarium for gastric cancer, with a plethora of clinical trials currently underway [40]. Our study found that immunotherapy was more commonly used in the treatment of intestinal adenocarcinomas than in mucinous

Table 3 Multivariate Cox Hazard analysis for 3- and 5-year survival among patients on ICI, n=200

Variable	3-year survival		5-year survival	
	Hazard ratio	P-value	Hazard ratio	P-value
Age	0.9 (0.9-0.9)	0.006*	0.9 (0.9-0.9)	0.018*
HP+ vs. *HP-*	2.0 (1.0-4.0)	0.041*†	1.5 (0.8-2.6)	0.224
Diffuse vs. intestinal adenocarcinoma	0.4 (0.2-0.9)	0.042*	0.5 (0.2-0.9)	0.049*
Race: Asian vs. non-Asian‡	0.7 (0.4-1.3)	0.239	-	-
Presence of other cancers (concurrent or preceding gastric cancer)‡	1.4 (0.7-2.8)	0.292	-	-

*Significant at the P<0.05 level

†Running the same analysis for patients not on ICI, findings were similar except for HP seropositivity, which was no longer significant (P=0.325)

‡These variables were excluded from the analysis at 5-years given their lack of significance at the 3-year analysis

ICI, immune checkpoint inhibitors; HP, Helicobacter pylori

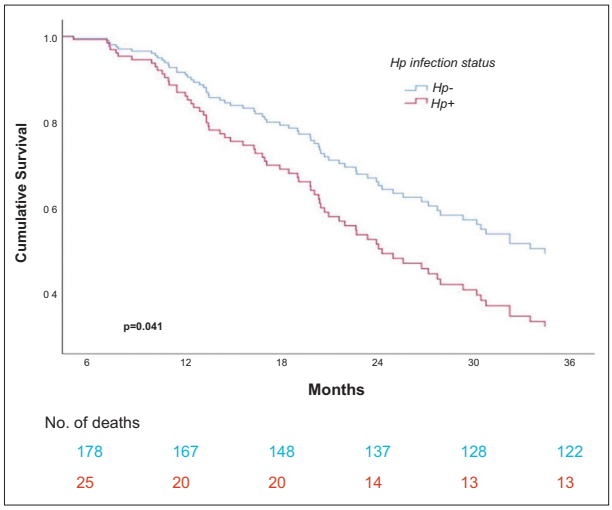

Figure 3 Cox survival curve for 3-year survival based on *Helicobacter pylori (Hp) pylori* status among patients receiving immune checkpoint inhibitors

disease; this was probably a spurious finding, considering that the choice of treatment does not differentiate between the two. However, multiple studies have found that diffuse subtypes may have higher PD-L1 expression than intestinal subtypes [11,41]. In this case, our findings further highlight the need to distinguish between the 2 subtypes when it comes to treatment.

The influence of *H. pylori* infection on the efficacy of ICIs is relatively understudied. A current hypothesis is that *H. pylori* virulence factors impair the effector functions of $CD4^+$ T cells and macrophages and promote the generation of inhibitory regulatory T cells [42]. Moreover, *H. pylori* induces the expression of PD-L1, further depleting the immune system and promoting immune evasion of the bacteria [16,43]. This directly antagonizes the mechanism of action of ICIs, especially anti–PD-1/L1 agents, and while many pre-clinical studies have demonstrated the immunosuppressive capacity of *H. pylori* infection, very few animal studies have explored its effect on immunotherapy [18,44]. The primary study by Oster *et al* demonstrated that tumor volumes of ICI-treated mice were larger among *H. pylori*-positive mice compared to *H. pylori*-negative mice [18]. The group was also able to show a detrimental effect on survival of patients with non-small cell lung cancer and *H. pylori* seropositivity. Since their initial publication, only 2 studies have been conducted to explore this topic in a real-world population [45,46]. All 3 studies showed worse overall and progression-free survival among *H. pylori*-positive patients with non-small cell lung cancer, melanoma or gastric cancers, while a recent meta-analysis of them confirmed this finding (n=263) [47]. These studies also showed that *H. pylori* eradication may not impact this association, similar to our findings. We did not explore progression-free survival in our study, yet we found a similar decline in overall survival among *H. pylori*-positive patients with gastric cancer in our study, with a sample size of around 200. Importantly, patients with *H. pylori* in our cohort were significantly more likely to be Asian than White. Previous research has shown that Asian patients have better gastric cancer survival than White patients [48]. The fact that *H. pylori*-positive patients receiving ICIs had worse overall survival despite this protective factor further supports our findings. Altogether, our results have significant clinical implications, as *H. pylori* infection may be a useful prognostic marker for the future success of immunotherapy, and it may be worth including *H. pylori* testing as part of the baseline pre-ICI evaluation. More studies are needed, however, to explore the utility of *H. pylori* eradication in preventing its detrimental impact on immunotherapy.

This study had several limitations. First, it was a retrospective single-center study, which limited our data collection to the available information documented in the electronic health records. Second, we had to limit the quantity of details we could collect from each chart review, given our very large sample size, which may have led to some important clinical variables being left out, such as tumor PD-1/L1 expression, tumor staging and surgical treatments performed. Additionally, it is difficult to accurately gauge

the prevalence of *H. pylori* infection, since this study was conducted at a tertiary care cancer center, so most patients received their diagnosis at an outside institute. Of those who were evaluated with biopsy upon cancer diagnosis, many cases may have been missed because of the unavoidable bias related to endoscopic sampling of neoplastic lesions, which have a high prevalence of necrosis. Given the difficulties of identifying *H. pylori* infection, we had to use more flexible criteria in defining the diffuse cancer subgroup, leading to a much higher prevalence than what is typically reported. Also, for this reason, we had to include cases who were seropositive, but who may not have had active infection, which is a common limitation of research on this subject. In a similar vein, while many of the *H. pylori*-negative patients were confirmed on gastric biopsy, many were considered negative given the absence of testing. However, this may overestimate the number of *H. pylori*-negative patients as some may have been asymptomatic carriers. Furthermore, it is difficult to establish the temporality of *H. pylori* serostatus, especially in relation to the initiation of immunotherapy, because of the limited documentation of exact dates in many cases. As a result, we can only know whether patients had the bacteria at some point, but it is conceivable that the timing of infection in relation to immunotherapy could also play a role in its detrimental effects—a factor that we were unable to study here. Finally, we restricted our sample to patients with gastric adenocarcinomas. Therefore, we cannot be sure whether our results generalize to patients with other types of gastric cancer receiving ICIs, or to immunotherapy for cancer in general.

Our study is one of the largest to date exploring the interaction between *H. pylori* status and immunotherapy effectiveness in a real-world population. *H. pylori* infection could potentially dampen the therapeutic effects of immunotherapy in patients with gastric cancer and lead to worse overall survival at 3 years in this population. *H. pylori* status does not seem to impact the survival of patients who are not receiving ICIs. Moreover, there may be an effect of gastric cancer subtype on patient survival, which may also be mediated by *H. pylori* status. Together, these findings suggest that testing for *H. pylori* could be a promising tool to predict the success of future immunotherapy, or the lack thereof, among patients who test positive for the bacteria, while the gastric cancer subtype may also help stratify patients. Future studies are needed to allow us to generalize these results to other cancer types and validate these findings.

Acknowledgments

Medical editing of this paper was provided by Ashli Nguyen-Villarreal, Associate Scientific Editor, and Bryan Tutt, Scientific Editor, Research Medical Library, The University of Texas MD Anderson Cancer Center.

Summary Box

What is already known:

- Gastric cancer is a significant cause of morbidity and mortality globally and is commonly treated with immune checkpoint inhibition (ICI), particularly with PD-1/L1 agents
- *Helicobacter pylori* (*H. pylori*) is one of the strongest risk factors for gastric cancer, and induction of PD-1 expression in immune cells may be a significant pathway in its carcinogenicity
- It has been suggested that *H. pylori* may decrease the efficacy of anti-PD1 blockade in the treatment of cancer, although evidence for this remains limited

What the new findings are:

- Prior or active infection with *H. pylori* may be associated with worse overall survival among gastric cancer patients treated with ICI
- The impact of *H. pylori* infection on survival may also depend on the subtype of gastric cancer
- No such associations between *H. pylori* and survival were noted among patients not receiving ICI therapy

References

1. Rawla P, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. *Prz Gastroenterol* 2019;**14**:26-38.
2. Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. *Lancet* 2020;**396**:635-648.
3. Schistosomes, liver flukes and *Helicobacter pylori*. *IARC Monogr Eval Carcinog Risks Hum* 1994;**61**:1-241.
4. Amieva M, Peek RM Jr. Pathobiology of *Helicobacter pylori*-induced gastric cancer. *Gastroenterology* 2016;**150**:64-78.
5. Ford AC, Yuan Y, Moayyedi P. *Helicobacter pylori* eradication therapy to prevent gastric cancer: systematic review and meta-analysis. *Gut* 2020;**69**:2113-2121.
6. Mungazi SG, Chihaka OB, Muguti GI. Prevalence of *Helicobacter pylori* in asymptomatic patients at surgical outpatient department: Harare hospitals. *Ann Med Surg (Lond)* 2018;**35**:153-157.
7. Guevara B, Cogdill AG. *Helicobacter pylori*: a review of current diagnostic and management strategies. *Dig Dis Sci* 2020;**65**: 1917-1931.
8. Ilic M, Ilic I. Epidemiology of stomach cancer. *World J Gastroenterol* 2022;**28**:1187-1203.
9. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand* 1965;**64**:31-49.
10. Petrelli F, Berenato R, Turati L, et al. Prognostic value of diffuse

versus intestinal histotype in patients with gastric cancer: a systematic review and meta-analysis. *J Gastrointest Oncol* 2017;**8**:148-163.
11. Tseng CH, Fang WL, Huang KH, et al. The clinicopathological characteristics and genetic alterations of mucinous carcinoma of the stomach. *J Chin Med Assoc* 2020;**83**:141-147.
12. Boku N, Satoh T, Ryu MH, et al. Nivolumab in previously treated advanced gastric cancer (ATTRACTION-2): 3-year update and outcome of treatment beyond progression with nivolumab. *Gastric Cancer* 2021;**24**:946-958.
13. Fuchs CS, Doi T, Jang RW, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. *JAMA Oncol* 2018;**4**:e180013.
14. Sun JM, Shen L, Shah MA, et al; KEYNOTE-590 Investigators. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. *Lancet* 2021;**398**:759-771.
15. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet* 2021;**398**:27-40.
16. Shen B, Qian A, Lao W, et al. Relationship between *Helicobacter pylori* and expression of programmed death-1 and its ligand in gastric intraepithelial neoplasia and early-stage gastric cancer. *Cancer Manag Res* 2019;**11**:3909-3919.
17. Kim W, Chu TH, Nienhüser H, et al. PD-1 signaling promotes tumor-infiltrating myeloid-derived suppressor cells and gastric tumorigenesis in mice. *Gastroenterology* 2021;**160**:781-796.
18. Oster P, Vaillant L, Riva E, et al. *Helicobacter pylori* infection has a detrimental impact on the efficacy of cancer immunotherapies. *Gut* 2022;**71**:457-466.
19. Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 2006;**118**:3030-3044.
20. Toh JW, Wilson RB. Pathways of gastric carcinogenesis, *Helicobacter pylori* virulence and interactions with antioxidant systems, vitamin C and phytochemicals. *Int J Mol Sci* 2020;**21**:6451.
21. Correa P, Houghton J. Carcinogenesis of *Helicobacter pylori*. *Gastroenterology* 2007;**133**:659-672.
22. Takahashi-Kanemitsu A, Knight CT, Hatakeyama M. Molecular anatomy and pathogenic actions of *Helicobacter pylori* CagA that underpin gastric carcinogenesis. *Cell Mol Immunol* 2020;**17**:50-63.
23. Segal ED, Cha J, Lo J, Falkow S, Tompkins LS. Altered states: involvement of phosphorylated CagA in the induction of host cellular growth changes by *Helicobacter pylori*. *Proc Natl Acad Sci U S A* 1999;**96**:14559-14564.
24. Rehman AU, Rahman MU, Khan MT, et al. The landscape of protein tyrosine phosphatase (Shp2) and cancer. *Curr Pharm Des* 2018;**24**:3767-3777.
25. Higashi H, Tsutsumi R, Muto S, et al. SHP-2 tyrosine phosphatase as an intracellular target of *Helicobacter pylori* CagA protein. *Science* 2002;**295**:683-686.
26. Wei J, Nagy TA, Vilgelm A, et al. Regulation of p53 tumor suppressor by *Helicobacter pylori* in gastric epithelial cells. *Gastroenterology* 2010;**139**:1333-1343.
27. Matsumoto Y, Marusawa H, Kinoshita K, et al. *Helicobacter pylori* infection triggers aberrant expression of activation-induced cytidine deaminase in gastric epithelium. *Nat Med* 2007;**13**:470-476.
28. Waldum HL, Fossmark R. Types of gastric carcinomas. *Int J Mol Sci* 2018;**19**:4109.
29. Qiu MZ, Cai MY, Zhang DS, et al. Clinicopathological characteristics and prognostic analysis of Lauren classification in gastric adenocarcinoma in China. *J Transl Med* 2013;**11**:58.
30. Fujii Y, Yoshihashi K, Suzuki H, et al. CDX1 confers intestinal phenotype on gastric epithelial cells via induction of stemness-associated reprogramming factors SALL4 and KLF5. *Proc Natl Acad Sci U S A* 2012;**109**:20584-20589.
31. Hooi JKY, Lai WY, Ng WK, et al. Global prevalence of *Helicobacter pylori* infection: systematic review and meta-analysis. *Gastroenterology* 2017;**153**:420-429.
32. Kim K, Chang Y, Ahn J, et al. Body mass index and risk of intestinal metaplasia: a cohort study. *Cancer Epidemiol Biomarkers Prev* 2019;**28**:789-797.
33. Huang RJ, Choi AY, Truong CD, Yeh MM, Hwang JH. Diagnosis and management of gastric intestinal metaplasia: current status and future directions. *Gut Liver* 2019;**13**:596-603.
34. Ajani JA, D'Amico TA, Bentrem DJ, et al. Gastric Cancer, Version 2.2022, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2022;**20**:167-192.
35. Stiekema J, Cats A, Kuijpers A, et al. Surgical treatment results of intestinal and diffuse type gastric cancer. Implications for a differentiated therapeutic approach? *Eur J Surg Oncol* 2013;**39**: 686-693.
36. Ajani JA, Rodriguez W, Bodoky G, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. *J Clin Oncol* 2010;**28**:1547-1553.
37. Narahara H, Iishi H, Imamura H, et al. Randomized phase III study comparing the efficacy and safety of irinotecan plus S-1 with S-1 alone as first-line treatment for advanced gastric cancer (study GC0301/TOP-002). *Gastric Cancer* 2011;**14**:72-80.
38. Yamaguchi K, Tada M, Horikoshi N, et al; Paclitaxel Gastric Cancer Study Group in Japan. Phase II study of paclitaxel with 3-h infusion in patients with advanced gastric cancer. *Gastric Cancer* 2002;**5**:90-95.
39. Kato K, Chin K, Yoshikawa T, et al. Phase II study of NK105, a paclitaxel-incorporating micellar nanoparticle, for previously treated advanced or recurrent gastric cancer. *Invest New Drugs* 2012;**30**:1621-1627.
40. Li K, Zhang A, Li X, Zhang H, Zhao L. Advances in clinical immunotherapy for gastric cancer. *Biochim Biophys Acta Rev Cancer* 2021;**1876**:188615.
41. Chen MH, Fang WL, Hung YP, Chao Y. Mucinous gastric adenocarcinoma: a good candidate for immune therapy? *J Chin Med Assoc* 2020;**83**:624-625.
42. Moyat M, Velin D. Immune responses to *Helicobacter pylori* infection. *World J Gastroenterol* 2014;**20**:5583-5593.
43. Holokai L, Chakrabarti J, Broda T, et al. Increased programmed death-ligand 1 is an early epithelial cell response to *Helicobacter pylori* infection. *PLoS Pathog* 2019;**15**:e1007468.
44. Oster P, Vaillant L, McMillan B, Velin D. The efficacy of cancer immunotherapies is compromised by *Helicobacter pylori* infection. *Front Immunol* 2022;**13**:899161.
45. Tonneau M, Nolin-Lapalme A, Kazandjian S, et al. *Helicobacter pylori* serology is associated with worse overall survival in patients with melanoma treated with immune checkpoint inhibitors. *Oncoimmunology* 2022;**11**:2096535.
46. Che H, Xiong Q, Ma J, et al. Association of *Helicobacter pylori* infection with survival outcomes in advanced gastric cancer patients treated with immune checkpoint inhibitors. *BMC Cancer* 2022;**22**:904.
47. Noori M, Fayyaz F, Rezaei N. Impact of *Helicobacter pylori* infection on the efficacy of immune checkpoint inhibitors for cancer treatment: a meta-analysis. *Immunotherapy* 2023;**15**:657-667.
48. Jin H, Pinheiro PS, Callahan KE, Altekruse SF. Examining the gastric cancer survival gap between Asians and whites in the United States. *Gastric Cancer* 2017;**20**:573-582.

Supplementary material

Supplementary Table 1 Demographic characteristics, n=2930

Characteristic	No. (%)		P-value
	HP⁻ N=2734	*HP*⁺ N=196	
Age, years, median (IQR)	61.6 (51.6-70.6)	58.5 (49.8-68.4)	0.015*
Male sex	1812 (66.3%)	110 (56.1%)	0.005*
Race			
White	1804 (66.0%)	78 (39.8%)	<0.001*
Asian	191 (7.0%)	42 (21.4%)	<0.001*
Cancer grade			0.464
I	199 (14.7%)	20 (17.2%)	
II	195 (14.4%)	20 (17.2%)	
III	253 (18.7%)	16 (13.8%)	
IV	703 (52.1%)	60 (51.7%)	
Gastric cancer subtype			0.017*
Intestinal adenocarcinoma	1782 (65.2%)	111 (56.6%)	
Diffuse adenocarcinoma	952 (34.8%)	85 (43.4%)	
Presence of other cancers	32 (1.2%)	2 (1.0%)	>0.99
Received ICI	180 (6.6%)	26 (13.3%)	0.001*
Duration of ICI therapy, days, median (IQR)	63 (21-148)	109 (30-343)	0.086
ICI type – n=206			0.441
Anti-PD-1/L1 inhibitor	153 (85.0%)	25 (96.2%)	
Anti-CTLA-4 inhibitor	4 (2.2%)	0 (0%)	
Combination therapy	23 (12.8%)	1 (3.8%)	
All-cause mortality	845 (30.9%)	78 (39.8%)	0.011*
Duration of follow up, years, median (IQR)	1.4 (0.7-2.9)	1.8 (1.0-3.6)	0.003*

HP, helicobacter pylori; ICI, immune checkpoint inhibitor; IQR, interquartile range

Supplementary Table 2 Chi square test for association between *HP* infection and ICI use

HP status	Received ICI	Did not receive ICI
HP+	26 (13.3%)	170 (86.7%)
HP-	180 (6.6%)	2554 (93.4%)

P<0.001

HP, Helicobacter pylori; ICI, immune checkpoint inhibitor

Supplementary Table 3 Univariate Cox regression analysis for 5- and 10- year survival

Variable	5- year survival		10-year survival	
	Odds ratio	P-value	Odds ratio	P-value
HP vs. no HP	1.2 (0.9-1.5)	0.093	1.2 (1.0-1.5)	0.017*
Diffuse adenocarcinoma vs. intestinal adenocarcinoma	0.8 (0.7-0.9)	0.024*	0.9 (0.8-1.1)	0.344
Receiving ICI vs. no ICI	2.1 (1.7-2.6)	<0.001*	1.7 (1.4-2.1)	<0.001*
Age	0.9 (0.9-0.9)	<0.001*	0.9 (0.9-0.9)	<0.001*
Male vs. female	1.0 (0.9-1.1)	0.929	0.9 (0.8-1.1)	0.534
Race: African American vs. Asian	0.7 (0.5-0.9)	0.003*	0.7 (0.6-0.9)	0.001*
Race: White vs. Asian	0.9 (0.8-1.1)	0.626	0.9 (0.8-1.0)	0.196
Previous or concurrent non-gastric cancers	1.7 (1.1-2.9)	0.027*	1.2 (0.7-1.9)	0.491
HP eradication	0.7 (0.2-1.7)	0.390	0.6 (0.2-1.5)	0.254

*Significant at the P<0.05 level

HP, Helicobacter pylori; ICI, immune checkpoint inhibitor

Supplementary Table 4 Multivariate Cox Hazard analysis for 10-year survival among patients with and without HP

Variable	No HP N=2734		HP N=195	
	Hazard ratio	P-value	Hazard ratio	P-value
Diffuse adenocarcinoma vs. intestinal adenocarcinoma	0.9 (0.8-1.0)	0.120	0.5 (0.2-0.8)	0.013*
Receiving ICI vs. no ICI	1.8 (1.4-2.3)	<0.001*	2.2 (1.2-4.2)	0.006*
Age	0.9 (0.9-0.9)	<0.001	0.9 (0.9-0.9)	0.006*

*Significant at the P<0.05 level

HP, Helicobacter pylori; ICI, immune checkpoint inhibitor