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Relationship between clinicopathological features and *Helicobacter pylori* infection status and prognosis of gastric cancer in a region of Southwest Algeria.

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Abstract

Background: Previous research has explored the association between *Helicobacter pylori* (*H.pylori*) infection and Gastric Cancer(GC). **Objectives**: The aim of this study was to investigate the impact of *H.pylori* status on the clinicopathological features and prognosis of gastric cancer patients in El-Bayadh region. **Methods:** Totally 126 patients diagnosed with gastric carcinoma at the Oncology Department of the EPH "Mohamed Boudiaf" in El-Bayadh between January 2015 and December 2022 were retrospectively analyzed**.** The relationship between *H.pylori* infection status, clinicopathological parameters, and survival time of GC was examined. **Results:** This study included 126 cases, of which 100 (79.36%) were *H. pylori*-positive, while 26 (20.64%) were negative. *H.pylori* infection was more prevalent in men (54 cases)(***p*=0.03**) and older individuals (82 cases). Gastric carcinoma with *H.pylori*-positive status showed predominantly intestinal and diffuse adenocarcinoma (***p*=0.002**). A statistically significant correlation emerged between *H.pylori* positive patients and lymph node metastasis (***p*=0.01**) and HER2 overexpression (***p*=0.05**). Overall survival (OS) correlated with *H.pylori* infection status, with H.pylori-negative patients tending to survive longer than positive ones (***p*= 0.03**) **Conclusion**: Our study suggests that *H.pylori* infection is a major risk factor for gastric cancer in our population, but there are also other factors involved in the development and progression of this disease.

Keywords:, *Helicobacter pylori* , Gastric cancer, clinicopathological, survival

Background

Gastric cancer (GC) is a public health problem worldwide[1], it is considered the fifth most commonly diagnosed cancer worldwide and the third most common cause of cancer related death[2]. Every year, approximately one million new cases of GC are diagnosed worldwide, its incidence varies according to geographical regions[1]. However, risk factors for tumors were different, recognized causes of GC include *Helicobacter pylori* (*h.pylori*) infection (the primary risk factor), gastric ulcer disease, gastroesophageal reflux disease, obesity, cigarette smoking, or metals, intake of high-salt foods, coffee, alcohol, gastric surgery, radiation exposure, and Epstein-Barr virus infection[3]. *H.pylori* is a gram-negative bacillus that resides in the gastric mucosa, causing chronic inflammation[4]. *H.pylori* infection is one of the most important factors involved in stomach canceration. The incidence of GC and peptic ulcers increases with the increase of *H.pylori* infection rate[5]. In 1994, the World Health Organization(WHO) declared that *H. pylori* was a causative agent of GC[6]. At present, the pathogenesis of GC has not yet been clarified, there is no convincing data for the relationship between *H.pylori* infection and tumor development and prognosis[7]. Furthermore, Studies indicate that *H.pylori* can instigate inflammatory reactions, resulting in damage to the gastric mucosa by influencing specific signaling pathways. Consequently, this may have implications for the prognosis of GC patients[8]. In recent studies, it has been suggested that H. pylori infection may also be linked to the prognosis of gastric cancer GC. Some research has indicated that patients who test positive for *H.pylori* exhibit better overall survival (OS) rates compared to those who test negative[9].Our aim in this study was to investigate the impact of *H.pylori* status on the clinicopathological features of GC patients in El-Bayadh region (Algeria). In addition, we compared the overall survival (OS) between the *H.pylori*-positive group and the *H.pylori*-negative group.

Methods

Data Collection

This retrospective study was conducted in the Oncology Department of the EPH "Mohamed Boudiaf" in El-Bayadh (Southwest Algeria). A total of 126 patients (74 men and 52 women) who were histologically diagnosed with GC between January 2015 and December 2022 were included in the study. The patients were divided into two groups according to their *H. pylori* status: negative

and positive. Clinical and pathological parameters such as age, gender, tumor location, histological classification, pathological TNM stage, lymphovascular invasion status, and HER2 overexpression were examined and recorded from medical charts or pathology reports for both groups. The difference in overall survival (OS) between the *H. pylori*-positive group and the *H. pylori*-negative group was compared. The study was conducted with prior approval from the institution where it was carried out, ensuring ethical standards were met.

Detection of *H. pylori* status

The status of *H. pylori* infection was assessed through histologic examination, serologic evaluation, and rapid urease test. Patients with a positive result in any of these tests were categorized as *H.pylori*-positive, while those with negative results in all three tests were considered *H.pylori*-negative.

Statistical analyses

SPSS26.0(Statistical Package for the Social Sciences, IBM Corporation; Chi-cago, IL. May 2019) was used for statistical analysis of data. The association between *H-pylori* infection status and clinicopathological features was compared using Pearson Chi-square test. The survival curves were plotted using Kaplan-Meier method and compared by the Log Rank test between patients of *H. pylori* positive and negative. $P < 0.05$ was considered statistically significant.

Results

Clinicopathological parameters of GC

The clinicopathological characteristics of the 126 patients included in this study are shown in Table 1. The patients' age at diagnosis ranged from 22 to 85 years, with a mean age of 61.97 ± 15.45 years. Males were the most affected, with a rate of 58.73% compared to 41.27% for females, resulting in a sex ratio of 1.42. Tumor size was (≥2 cm) in 93 cases (82.30%) and (<2 cm) in 20 cases (17.70%), ranging from 0.4 to 12 cm, with an average size of 4.82 cm. Lauren's intestinal histological subtype was the most frequently diagnosed, accounting for 65 cases (51.59%). Diffuse and mixed subtypes were observed in 38 cases (30.16%) and 23 cases (18.25%), respectively. Out of all the cases, 49.21%, 22.22%, 15.87%, and 12.7% were in pathological stages III, II, IV, and I, respectively. Most of the tumors (77.47%) were in stage T3 and T4, whereas 6.31% of the cases

were in the early stage T1. Regarding lymph node status, 90 tumors (81.08%) were lymph node positive, while 21 (18.92%) were node negative.

Relationship between *H.pylori* infection status and clinicopathological features of GC

The association between *H.pylori* infection and clinicopathological features is summarized in Table 2. One hundred (79.36%) out of 126 patients who underwent surgery for GC were *H. pylori*-positive, while 26 (20.64%) were negative. *H.pylori* infection was more frequently observed in men (54 cases) and older patients (82 cases). However, no significant difference was found between the H. pylori-negative and positive groups regarding tumor diameter (p=0.96). Regarding histological classification, GC with *H.pylori* positivity predominantly exhibited intestinal and diffuse adenocarcinoma according to the Lauren's classification (***p*=0.002**). According to the pTNM classification, *H.pylori*-positive tumors were diagnosed at an advanced stage of the disease, mainly in the pT3-T4 category (76 cases, 88.37%). A statistically significant correlation was observed between *H.pylori*-positive patients and lymph node metastasis, with 82 (91.11%) cases showing metastasis (***p*=0.01**). However, *H.pylori* infection status did not significantly correlate with tumor grade and distant metastasis (p>0.05). Immunostaining of the HER2 (human epidermal growth factor receptor 2) receptor was detected in 49 (38.88%) cases. Overexpression of HER2 was positive in 10 (20.40%) cases and negative in 39 (79.60%) cases, showing a significant correlation with *H.pylori* infection status (***p*=0.05**).

Table 1: Clinicopathological characteristics of the patients in the present study.

Variety	**Overall n=126**
Age at diagnosis	
<50 years	24(19.04)
≥50 years	102(80.96)
Gender	
Male	74(58.73)
Female	52(41.27)
Tumor size	
<2 cm	20(17.70)
≥2 cm	93(82.30)
Histological subtype	
Intestinal	65(51.59)
Mixed	23(18.25)
Diffuse	38(30.16)
Histological grade	
I	16(12.7)
II	28(22.22)
III	62(49.21)
IV	20(15.87)
pT status	
pT1	7(6.31)
pT2	18(16.22)
pT3	58(52.25)
pT4	28(25.22)
Lymph node metastasis	
No	21(18.92)
Yes	90(81.08)
Distant metastasis	
No	87(78.38)
Yes	24(21.62)

H.pylori infection and survival

The relationship between GC survival and relative *H.pylori* infection was investigated using Kaplan-Meier survival analysis (figure 1), which indicated that *H.pylori* infection was associated with lower survival rates among GC patients. In our study cohort, the mean survival time of the *H.pylori*-negative group was 68 months (95% CI=[53.44-82.49]), while 39.56 months (95% CI=[30.71-48.40]) was observed in the *H pylori*-positive group. Importantly, the survival curve of *H.pylori*-positive patients was worse than that of *H.pylori*-negative patients; the difference between the two groups was statistically significant (***p*=0.03**).

Table 2: Association Between *H.pylori* status and Clinicopathological features.

Variety	H.pylori negative 26(20.64 %)	H.pylori positive 100(79.36%)	***P*** value
Age at diagnosis			
≥50 years	20(19.6)	82(80.4)	*p*=0.55
<50 years	6(25)	18(75)	
Gender			
Male	20(27)	54(73)	***p*=0.03**
Female	6(11.5)	46(88.5)	
Tumor size			
<2 cm	4(20)	16(80)	*p*=0.96
≥2 cm	19(20.44)	74(79.56)	
Lauren's classification			
Intestinal	19(29.24)	46(70.76)	***p*=0.002**
Mixed	7(30.44)	16(69.56)	
Diffuse	0(0)	38(100)	
Histological grade			
I	8(50)	8(50)	*p*=0.13
II	6(21.43)	22(78.57)	
III	8(12.9)	54(87.1)	
IV	4(20)	16(80)	
pT status			
pT1-T2	4(16)	21(84)	*p*=0.56
pT3-T4	10(11.63)	76(88.37)	
Lymph node metastasis			
No	6(28.57)	15(71.43)	***p*=0.01**
Yes	8(8.89)	82(91.11)	
Distant metastasis			
No	11(12.65)	76(87.35)	*p*=0.98
Yes	3(12.5)	21(87.5)	
HER2 status			
negative	11(28.21)	28(71.79)	***p*=0.05**
Positive	0(0)	10(100)	

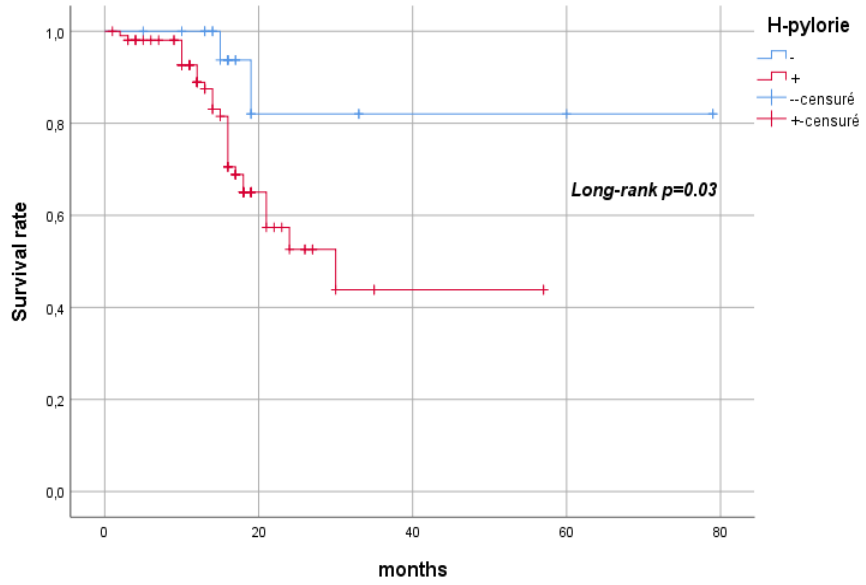

Figure1: Kaplan-Meier curves for the GC survival rate of *H.pylori* positive and negative patients.

Discussion

H.pylori infection is one of the most significant risk factors for GC development[10]. The bacterium infects the gastric mucosa, leading to chronic gastritis, which can progress to atrophic gastritis, intestinal metaplasia, dysplasia, and eventually gastric adenocarcinoma in some individuals[11]. The World Health Organization (WHO) has categorized *H.pylori* as a group 1 carcinogen[12]. Recent research also noted a significantly higher rate of *H.pylori* positivity among GC patients compared to non tumor controls[13]. Previous studies[14,15] investigating GC have hinted at a potential correlation between *H.pylori* status and prognosis, yet definitive conclusions on this association remain elusive.

In the present study, the *H.pylori* infection was positive in 100(79.36%) and negative in 26 (20.64%) cases. The occurrence of *H.pylori* infection and GC has been documented at varying frequencies across different studies. Jia et *al* found that *H.pylori* infection was present in 69.4%% of GC cases[16], Selcukbiricik et *al* reported it in **54%** of cases[17], while Kayapinar observed it in 45% of patients with GC[18]. These variations could stem from several factors, including dietary patterns, socioeconomic factors, and racial disparities.

Of the 100 *H.pylori*-positive tumors in the present study, 46 were intestinal type ,38 and 16 cases were diffuse and mixed type respectively according to Lauren's classification. These data are consistent with previous reports that the intestinal type showed a higher rate of *H.pylori* positivity than the diffuse/mixed type[16,19]. The colonization of *H.pylori* has been associated with the occurrence of intestinal metaplasia and dysplasia in precancerous lesions. Research indicates a close correlation between the development of intestinal-type adenocarcinoma and the presence of intestinal metaplasia[19,20]. On the other hand, *H.pylori* induced gastritis has been demonstrated to contribute to the formation of intestinal type GC by indirectly causing *p53* mutations[21].

The results of the current study indicate a statistically significant finding overexpression of HER2 was higher in the *H.pylori*-negative group than in the *H.pylori*-positive group, an observation concordant with the results of Sreeram et *al*, who were demonstrate that HER2 overexpression was observed in *H.pylori*-negative patients (5/26, 19.2%) compared to *H.pylori*-positive patient (4/59, 6.8%) (p=0.02). Conversely, Chao G et *al*, observed a difference in HER2 between the *H.pylori*-positive group and the *H.pylori*-negative group[22]. Furthermore, *H.pylori* infection was significantly correlated with HER2 index and presented a positive correlation. Tegtmeyer N et *al*, recorded that *H.pylori* infection leads to activation of receptor tyrosine kinases like HER2. They describe that this activation leads to epithelial cell scattering and increased mitotic activity in these cells[23].

The current study revealed a significant association between a more advanced pN stage and *H.pylori*-positive patients (p=0.01). Theory, the invasion and metastasis of tumors are associated with the matrix metalloproteinases (MMPs) secreted by the GC cells. These enzymes have the ability to break down the extracellular matrix, alter the composition of the vascular basement membrane and facilitate the invasion and metastasis of cancer cells[24,25]. After infecting the stomach, *H.pylori* can induce the release of MMP-1, MMP-2, MMP-3, and TIMP-3 from GC cells, potentially accelerating the progression of gastric cancer invasion and metastasis[26]. In our study, we found no significant correlation between the relative amount of *H.pylori* infection and age, gender, or distant metastasis. Other research[27,20] reported that age, tumor stage, tumor depth, and lymph node were prognostic factors based on both univariate and multivariate analyses. Interestingly, these prognostic factors showed no significant divergence between the *H.pylori* positive and negative groups, These findings are in line with the results of our study.

In the present study, when we investigated the influence of *H.pylori* infection on the overall survival of GC, the survival curve demonstrated that the mean survival time in the *H.pylori*-negative group was 68 months, with a 95% confidence interval between 53.44 and 82.49 months. This relatively long survival time suggests that patients infected with *H pylori* tend to survive longer. However, the mean survival time in the *H.pylori*-positive group was 39.56 months, with a 95% confidence interval between 30.71 and 48.40 months. This survival time is significantly (p=0.03) shorter than that of the *H.pylori*-negative group, indicating a positive impact of *H.pylori* infection on patient survival in our study cohort.

These results are in agreement with the data observed in a study conducted by Jia et *al*, which indicated that patients who tested negative for *H.pylori* showed a longer (OS) compared to those who tested positive. The estimated median survival was 17.5 months for the negative group versus 6.2 months for the positive group (p=0.021)[16].On the other hand, the study by Che et *al*[28], recently demonstrated that the *H.pylori* infection status did not emerge as an independent prognostic factor, as there was no distinction in the survival outcomes between patients with or without *H.pylori*. Nevertheless, upon further analysis of *H.pylori*-positive patients, it was noted that those with a higher number of *H.pylori* copies tended to have a more favorable prognosis compared to those with a lower number of copies[29,30].

Conclusion

GC is a multifactorial, multi-stage complex disease with marked heterogeneity. The high prevalence of *H.pylori* infection in GC patients highlights the need for further research and development of effective prevention and treatment strategies. Future research should focus on elucidating the molecular and cellular processes involved in the pathogenesis of *H.pylori* induced GC.

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