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Helicobacter Pylori Seropositivity in Patients with Ankylosing Spondylitis: What Does It Imply?

Firdevs Ulutaş, Veli Çobankara

Department of Internal Medicine, Division of Rheumatology, Pamukkale University, Faculty of Medicine, Denizli, Türkiye

Abstract:

Objective: This study investigates clinical factors associated with *Helicobacter pylori (H. pylori)* seropositivity in patients with ankylosing spondylitis (AS), a condition in which *H. PYLORI* has been underexplored.

Methods: AS patients meeting the modified New York criteria, aged 18-65 years, without comorbidities and followed between 2022 and 2023, were included. Serum anti-*H. pylori* IgG and IgA antibodies were measured using ELISA and categorized as negative, positive, or highly positive based on titer levels.

Results: The cohort consisted of 243 patients, 36.8% males and 63.2% females, with a mean age of 46.6 years and a mean disease duration of 7.9 years. Logistic regression analysis revealed that increasing age significantly elevated the risk of both IgG and IgA seropositivity. Elevated erythrocyte sedimentation rate was strongly associated with IgA positivity (Odds Ratio [OR]: 3.08, 95% Confidence Interval [CI]: 2.05-4.11), while hypomagnesemia (mean serum Mg: 1.95±0.09) also increased the likelihood of IgA seropositivity (OR: 2.82, 95% CI: 1.05-2.88). Notably, hip involvement emerged as a robust predictor of IgG seropositivity (OR: 3.48, 95% CI: 1.52-6.04), and a history of uveitis was linked to a 1.61-fold increased risk of IgG positivity.

Conclusion: The findings suggest that older AS patients with systemic inflammation or low magnesium levels are more likely to exhibit *H. pylori* infection. Moreover, hip involvement and uveitis may serve as relevant clinical markers warranting *H. pylori* screening in this population. These associations highlight potential pathogenetic links between microbial triggers and disease expression in AS.

Keywords: Helicobacter Pylori, Spondylitis Ankylosing, Inflammation, Uveitis, Hip Joint

Helicobacter pylori (H. pylori) is a gram negative bacteria that infects the gastric mucosa and commonly causes of gastritis, duodenal and/or gastric ulcers. Contaminated food and water, close contact with infected individuals, gastroesophageal reflux, intrafamilial transmission and smoking are risk factors for the infection [1]. A growing body of evidence, including a recently published systematic review and meta-analysis, has confirmed the strong link between *H. pylori* infection and the development of gastric cancer [2]. It has been emphasized that while the global prevalence of *H. pylori* infection has declined among adults over the past three decades, it has remained relatively unchanged in children and adolescents [3]. These findings may serve as a guide for emphasizing the importance of continuing *H. pylori* screening in younger populations, considering the spectrum of

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Corresponding author: Firdevs Ulutaş, MD., Assist. Prof., Phone: +90 258 296 20 00, E-mail: firdevsulutas1014@gmail.com

diseases associated with the infection.

H. pylori is increasingly studied as a trigger of autoimmunity, potentially contributing to diseases like lupus, rheumatoid arthritis, and Sjögren's syndrome via chronic inflammation, increased autoantibody production, and impaired immune tolerance [4]. Beyond autoimmune diseases, *H. pylori* infection has also been implicated in the pathogenesis of various other immune-mediated disorders, including inflammatory bowel disease and psoriasis. *H. pylori* and various other immune-mediated disorders may share common pathogenic mechanisms, including chronic inflammation, molecular mimicry, and alterations in mucosal immunity [5]. Among the most widely implicated mechanisms are molecular mimicry and alterations in mucosal immunity, both of which may contribute to the development of immune-mediated disorders in the context of *H. pylori* infection [6].

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease, mainly affecting young men. It is strongly linked to Human Leukocyte Antigen Class I Molecule B27 (HLA-B27) and influenced by gut dysbiosis, infections, and modifiable factors like smoking [7]. Various infectious agents particularly gastrointestinal and urogenital pathogens may significantly increase the risk of AS, supporting the hypothesis that infections could act as culprit triggers in genetically predisposed individuals [8]. A microbial diversity and composition, including a reduction in beneficial commensals and an increase in pro-inflammatory taxa may cause gut microbial imbalance and may contribute to the immunopathogenesis of AS [9].

A Danish cohort found higher AS prevalence in *H. pylori*-positive individuals. However, after 8 years, new AS cases were fewer among those previously *H. pylori*-positive, suggesting *H. pylori* eradication may have a protective role in AS pathogenesis [10]. Although *H. pylori* infection may promote systemic inflammation, prior studies show no consistent association with increased disease activity scores in affected patients [11]. Recent evidence links higher *H. pylori* seropositivity to poor Tumor necrosis factor (TNF) inhibitor response in AS, suggesting that chronic *H. pylori* infection may contribute to resistance to biologic therapies [12].

So, in light of current scientific data, the link between *H. pylori* infection and axial spondyloarthritis (auxSpA) is not definitively established. Is *H. pylori* infection a causative factor or merely an associated condition in individuals with spondyloarthritis (SpA)? The strength of the association also remains poorly defined. We aimed to identify disease-related determinants of *H. pylori* positivity among patients diagnosed with AS.

METHODS

Patient Selection

This is a retrospective cohort study conducted on patients who presented to the rheumatology outpatient clinic at Pamukkale University. Patients diagnosed with AS based on the modified New York classification criteria were enrolled in this study. Inclusion criteria comprised an age range of 18 to 65 years, consistent outpatient follow-up between 2022 and 2023, and the absence of comorbid conditions. Patients for whom *H. pylori* data were accessible were enrolled in the study. The medical records of these patients were retrospectively reviewed. From the patients' medical records, detailed information was extracted, including age, sex, demographic characteristics, treatment regimens, disease phenotypes, and the presence or absence of AS in first-degree relatives as reported family history.

Assessments

Conventional radiographs were available for all patients in the institutional system, whereas Magnetic resonance imaging (MRI) data were not consistently present. To ensure a homogeneous study population, only patients who met the modified New York criteria for AS based on radiographic findings were included. Patients classified as having non-radiographic axSpA were excluded from the study. All AS patients were classified in according to the modified New York classification criteria [13]. HLA-B27 was tested with flow cytometry according to the methods described by Albrecht and Muller [14]. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was used to evaluate disease activity [15]. To assess disease activity, patients were stratified into four groups according to their BASDAI scores. A BASDAI score of <2 was considered indicative of disease remission; scores between 2 and <4 were classified as low disease activity. Patients with scores between 4 and <6 were categorized as having moderate disease activity, while scores ≥6 were considered representative of high disease activity.

The presence of uveitis, psoriasis, hip joint involvement and inflammatory bowel disease was recorded based on documentation in the patients' medical records indicating that these conditions had been diagnosed, managed, or followed by relevant specialists (ophthalmology, dermatology, orthopedics, and gastroenterology, respectively). A history of any of these manifestations - regardless of whether they were active at the time of evaluation, their frequency, or whether they occurred only once - was considered positive.

Serum immunoglobulin G and immunoglobulin A antibodies to *H. pylori* were measured by enzyme-linked immunosorbent assay (ELİSA) [16]. Patients were classified according to *H. pylori* antibody titers (positive for ≥ 10 U/mL, high positive for ≥ 100 U/mL and negative for < 9.9 U/mL) [17].

Ethical approval for this non-interventional study was obtained from the Pamukkale University non-interventional clinical research ethics committee (approval number: 20, protocol code: 11/2019), granted on 19 November 2019.

Statistical Analysis

In the analysis of data, descriptive statistics, including mean, standard deviation, frequency, and percentage values, have been presented. To examine the measurements by groups, an Independent Samples t-test analysis was conducted. For the analysis of proportional variables, a Chi-square test was performed, with Fisher's correction applied when necessary. Logistic regression analysis was used to examine the impact of multiple risk factors on the positivity of anti-*H. pylori* Ig A and *H. pylori* Ig G. The logistic regression analysis was calculated adjusted for smoking, disease duration and sex factors. Odds ratio and 95% confidence interval were calculated for the risk factors. In this study, P-value<0.05 was considered statistically significant. Analyses were performed using SPSS 25.00.

TABLE 1. General Patient Characteristics and *H. Pylori* Ig A/ *H. Pylori* Ig G Positivity in the whole Study Group

Variables	Data
Gender	
Male	82 (36.8%)
Female	141 (63.2%)
Age (years))	46.59±11.97
Disease duration (years)	7.89±9.28
Smoking	
None	144 (64.6%)
Yes	79 (35.4%)
***H. pylori* Ig A positivity**	
Negative	128 (57.4%)
Positive	75 (33.6%)
High positive	20 (9.0%)
***H. pylori* Ig G positivity**	
Negative	96 (43.0%)
Positive	101 (45.3%)
High positive	26 (11.7%)

Data are shown as mean±standard deviation or n (%).
H. pylori, *helicobacter pylori*.

RESULTS

A total of 243 AS patients were included, of the patients, 36.8 % were male, and 63.2 % were female. The average age of the patients was 46.59±11.97 years, and the average disease duration was 7.89±9.28 years (Table 1). A Chi-square test indicated no significant effect of smoking, gender, HLA-B27 positivity, or other factors on *H. pylori* Ig A and *H. pylori* Ig G Positivity, except for uveitis and hip involvement, which showed significant associations with the presence of *H. pylori* Ig G positivity, shown in Table 2. No statistically significant association was observed between either *H. pylori* Ig A or *H. pylori* Ig G positivity and the type or frequency of analgesic or biologic agent use (Table 3). Among analgesics, diclofenac was the most commonly used drug across all subgroups. Meloxicam showed a slightly higher usage in *H. pylori* Ig A positive (8.4%) compared to *H. pylori* Ig A negative (3.1%) patients, although this difference did not reach statistical significance (P=0.23). Regarding biologic therapies, no significant

TABLE 2. Factors that related to *H. Pylori* Ig A/ *H. Pylori* Ig G Positivity

		***H. pylori* Ig A positivity**			***H. pylori* Ig G positivity**		
		Negative	**Positive**	**P-value**	**Negative**	**Positive**	**P-value**
Smoking, n (%)	No	77 (60.2)	67 (70.5)	0.07	59 (61.5)	85 (66.9)	0.24
	Yes	51 (39.8)	28 (29.5)		37 (38.5)	42 (33.1)	
Gender, n (%)	Male	47 (36.7)	35 (36.8)	0.58	36 (37.5)	46 (36.2)	0.48
	Female	81 (63.3)	60 (63.2)		60 (62.5)	81 (63.8)	
HLA B27 positivity, n (%)	No	57 (44.5)	43 (45.7)	0.48	40 (41.7)	60 (47.6)	0.23
	Yes	71 (55.5)	51 (54.3)		56 (58.3)	66 (52.4)	
Acute sacroiliitis at the diagnosis, n (%)	No	35 (27.3)	33 (34.7)	0.15	28 (29.2)	40 (31.5)	0.41
	Yes	93 (72.7)	62 (65.3)		68 (70.8)	87 (68.5)	
Family history, n (%)	No	72 (56.3)	60 (63.2)	0.18	56 (58.3)	76 (59.8)	0.46
	Yes	56 (43.8)	35 (36.8)		40 (41.7)	51 (40.2)	
Inflammatory bowel disease, n (%)	No	122 (95.3)	91 (95.8)	0.58	91 (94.8)	122 (96.1)	0.44
	Yes	6 (4.7)	4 (4.2)		5 (5.2)	5 (3.9)	
Uveitis, n (%)	No	111 (86.7)	84 (88.4)	0.43	87 (90.6)	108 (85)	**0.04***
	Yes	17 (13.3)	11 (11.6)		9 (9.4)	19 (15)	
Psoriasis, n (%)	No	124 (96.9)	94 (98.9)	0.29	94 (97.9)	124 (97.6)	0.63
	Yes	4 (3.1)	1 (1.1)		2 (2.1)	3 (2.4)	
Enthesitis, n (%)	No	73 (57)	59 (62.1)	0.27	57 (59.4)	75 (59.1)	0.54
	Yes	55 (43)	36 (37.9)		39 (40.6)	52 (40.9)	
Dactilitis, n (%)	No	125 (97.7)	94 (98.9)	0.43	93 (96.9)	126 (99.2)	0.21
	Yes	3 (2.3)	1 (1.1)		3 (3.1)	1 (0.8)	
Arthritis, n (%)	No	94 (73.4)	70 (73.7)	0.55	74 (77.1)	90 (70.9)	0.19
	Yes	34 (26.6)	25 (26.3)		22 (22.9)	37 (29.1)	
Hip involvement, n (%)	No	124 (96.9)	87 (91.6)	0.08	95 (99)	116 (91.3)	**0.02***
	Yes	4 (3.1)	8 (8.4)		1 (1)	11 (8.7)	
Dyspepsia, n (%)	No	95 (74.2)	72 (75.8)	0.43	75 (78.1)	92 (72.4)	0.49
	Yes	33 (25.8)	23 (24.2)		21 (21.9)	35 (27.6)	
BASDAI, n (%)	Remission	47 (36.7)	46 (48.4)	0.62	36 (37.5)	57 (44.9)	0.64
	Low	14 (10.9)	10 (10.5)		11 (11.5)	13 (10.2)	
	Moderate	24 (18.8)	12 (12.6)		15 (15.6)	21 (16.5)	
	High	43 (33.6)	27 (28.4)		34 (35.4)	36 (28.3)	

BASDAI, bath ankylosing spondylitis disease activity ındex; HLA B27, human leukocyte antigen B27; *H. pylori*, *Helicobacter pylori.* *Chi-square test. Statistically significant P-values are shown in bold.

TABLE 3. Distribution of analgesic and Biologic Therapy Usage According to *H. pylori* Ig A and *H. pylori* Ig G antibody seropositivity

		H. pylori Ig A		P-value	*H. pylori* Ig G		P-value
		Negative	Positive		Negative	Positive	
Analgesics, n (%)	None	6 (4.7)	6 (6.3)	0.23	6 (6.3)	6 (4.7)	0.29
	Diclofenac	55 (43)	37 (38.9)		46 (47.9)	46 (36.2)	
	Indomethacin	20 (15.6)	13 (13.7)		13 (13.5)	20 (15.7)	
	Asemetazin	18 (14.1)	13 (13.7)		13 (13.5)	18 (14.2)	
	Ibuprofen	10 (7.8)	9 (9.5)		9 (9.4)	10 (7.9)	
	Meloxicam	4 (3.1)	8 (8.4)		3 (3.1)	9 (7.1)	
	Other	15 (11.7)	9 (9.5)		6 (6.3)	18 (14.2)	
Biologic Therapies, n (%)	None	83 (64.8)	59 (62.1)	0.72	57 (59.4)	85 (66.9)	0.53
	Golimumab	7 (5.5)	2 (2.1)		5 (5.2)	4 (3.1)	
	Etanercept	10 (7.8)	8 (8.4)		12 (12.5)	6 (4.7)	
	Adalimumab	13 (10.2)	13 (13.7)		8 (8.3)	18 (14.2)	
	Certolizumab	8 (6.3)	7 (7.4)		7 (7.3)	8 (6.3)	
	Secukinumab	3 (2.3)	5 (5.3)		4 (4.2)	4 (3.1)	
	Infliximab	4 (3.1)	1 (1.1)		3 (3.1)	2 (1.6)	

H. pylori, helicobacter pylori.

differences were noted between groups.

A significant difference was found in age and erythrocyte sedimentation rate (ESR) levels in relation to *H. pylori* Ig A positivity. The magnesium levels were lower and ESR was higher in *H. pylori* Ig A positive patients compared to *H. pylori* Ig A negative patients. *H. pylori* Ig G positivity was also significantly associated with increased age and the hip involvement. The numerical data are presented in detail in Table 4.

The variables examined up to this point are those analyzed univariately. In Table 5, the risks and effects of the variables affecting *H. pylori* Ig A positivity are examined to determine whether they are the same. Logistic regression analysis indicated that ESR, age, and magnesium levels were significant risk factors for *H. pylori* Ig A positivity. Both of high ESR and elderly-age increased the likelihood of *H. pylori* Ig A positivity, and lower magnesium levels also increased the risk. The ability of the variables ESR, age, and magnesium levels to explain the risk of *H. pylori* Ig A positivity was found to be 29% (Neg. $R^2 = 0.29$). The model's success rate is 80%, which can be considered high. When interpreting the significant factors, it was found that high ESR levels (30.73±20.34 mm/h) increase the likelihood of *H. pylori* Ig A positivity by 3.08 times (95% confidence interval [CI]: 2.05-4.11). The increased age of patients (48.65±11.29 years) increases the likelihood of *H. pylori* Ig A positivity by 2.52 times (95% CI: 1.49-3.55). Lower magnesium levels in patients (1.95±0.09 mEq/L) increase the likelihood of *H. pylori* Ig A positivity by 2.82 times (95% CI: 1.05-2.88).

Upon reviewing the results, the logistic regression analysis for *H. pylori* Ig G positivity revealed that hip involvement, age, and uveitis were significant risk factors for *H. pylori* Ig G positivity ($P<0.05$). Age and uveitis increased the likelihood of *H. pylori* Ig G positivity (Table 6). The ability of the variables hip involvement, age, and the presence of uveitis to explain the risk of *H. pylori* Ig G positivity was found to be 25% (Neg. $R^2 = 0.25$). The model's success rate is 76%, which can be considered moderately high. When interpreting the significant factors, it was found

TABLE 4. Measures of Positivities of Antibodies of *H. Pylori* IgA and *H. Pylori* Ig G

	***H. pylori* IgA**			***H. pylori* Ig G**		
	Negative	**Positive**	**P-value**	**Negative**	**Positive**	**P-value**
Age (years)	45.07±12.28	48.65±11.29	**0.03***	44.89±12.3	47.89±11.6	**0.04***
Disease duration (years)	7.22±9.13	8.79±9.44	0.28	7.08±8.5	8.49±9.81	0.59
Glucose (mg/dL)	100.2±21.27	100.31±24.57	0.79	102.05±27.41	98.87±18.32	0.74
Creatinin (mg/dL)	0.71±0.17	0.73±0.17	0.31	0.71±0.18	0.72±0.16	0.33
ALT (U/L)	21.43±14.77	20.79±10.78	0.93	22.63±16.28	20.05±10.19	0.39
ESR (mm/h)	24.09±15.52	30.73±20.34	**0.01***	25.57±19.38	27.94±16.88	0.10
CRP (mg/dL)	5.24±7.57	4.57±5.18	0.71	5.52±7.93	4.53±5.49	0.28
Magnesium (mEq/L)	2.01±0.05	1.95±0.09	**0.03***	1.99±0.19	1.98±0.15	0.79
BASDAI	4.57±5.95	3.74±2.64	0.20	4.71±6.71	3.84±2.63	0.27

Data are shown as mean±standard deviation or n (%). ALT, alanine aminotransferase; BASDAI, bath ankylosing spondylitis disease activity index; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; *H. pylori*, *helicobacter pylori*. **Independent samples t-test analysis, *0.05: significant difference at the 0.05 level.
Statistically significant P-values are shown in bold.

that patients with hip involvement have a 3.48 times higher likelihood of *H. pylori* Ig G positivity (95% CI: 1.52-6.04). The higher age of patients (48.65±11.29 years) increases the likelihood of *H. pylori* Ig G positivity by 2.40 times (95% CI: 1.43-3.46). The presence of uveitis (1.95±0.09) increases the likelihood of *H. pylori* Ig G positivity by 1.61 times (95% CI: 1.05-2.22).

DISCUSSION

Through this retrospective cohort study, we have identified several potential associations between *H. pylori* seropositivity and AS, including anti-*H. pylori* Ig A (age, ESR, serum magnesium) and anti-*H. pylori* Ig G (age, uveitis, hip involvement). To the best of our knowledge, this study is the first to analyze the association between *H. pylori* and the characteristics of AS. One of the most intriguing findings of this study is that uveitis is associated with *H. pylori* Ig G seropositivity. Literature suggests that *H. pylori* infection is linked to undifferentiated anterior uveitis, while the data connecting *H. pylori* infection to AS remains conflicting. Otasevic et al. [18] explored the presence of *H. pylori* in patients with acute anterior uveitis (AAU) and SpA. All three patient groups (66.7% in the AAU group, 73.3% in the SpA group, and 80% in the AAU+SpA group) exhibited a higher percentage of *H. pylori* positivity compared to healthy controls, with only 26.7% of controls being anti-*H. pylori* positive, indicating a statistically significant difference between the patient and control groups (P<0.05) [18]. A prospective, cross-sectional, and

TABLE 5. Determination of Risk Levels for *H. pylori* Ig A Positivity

Variables	W	P-value	β (Risk level)	95% CI (β)
ESR	4.11	**0.03***	3.08	2.05-4.11
Age	3.42	**0.03***	2.52	1.49-3.55
Magnesium	2.12	**0.04***	1.82	1.05-2.88

CI, confidence Interval for the risk level; ESR, eruthrocyte sedimentation rate; *H. pylori*, *helicobacter pylori*
*Logistic regression analysis, significant risk factors β=risk level. Statistically significant P-values are shown in bold.

TABLE 6. **Determination of Risk Levels for *H. Pylori* Ig G Positivity**

Variables	W	P-value	β (Risk level)	95% CI (β)
Hip Involvement	5.58	**0.04***	3.48	1.52–6.04
Age	3.12	**0.04***	2.40	1.43–3.46
Uveitis	3.52	**0.04***	1.61	1.05–2.22

CI, confidence interval for the risk level; *H. pylori*, *helicobacter pylori*

*Logistic regression analysis, significant risk factors β=risk level. Statistically significant P-values are shown in bold.

comparative study also demonstrated a direct association between undifferentiated non-granulomatous uveitis and *H. pylori* Ig G titers [19]. Although the seroprevalence of *H. pylori* in uveitis has been reported to be increased in several studies, the potential role of *H. pylori* in the pathogenesis of uveitis remains unclear [20]. In our study, this may indicate a comorbidity or even an interaction, suggesting that AS patients with concomitant *H. pylori* infection are more likely to develop uveitis. Given that patients with prior experiences of uveitis and a higher number of uveitis flares were not included in this study, establishing a clear cause-and-effect relationship is challenging retrospective studies. In addition to uveitis, hip involvement was also found to be related to *H. pylori* Ig G positivity in our study. While no direct studies have yet explored the association between *H. pylori* seropositivity and hip joint involvement in AS, the existing evidence supports a potential link between chronic infections and more severe disease phenotypes. Given that hip involvement is considered a marker of advanced or refractory AS, it is plausible to hypothesize that *H. pylori* -related systemic inflammation may contribute to such clinical manifestations. It remains unclear to what extent the longer disease duration, more frequent exposure to medications, and older patient population may have contributed to the observed high prevalence. Furthermore, the limited number of patients exhibiting hip involvement (n=24) substantially hindered the ability to conduct a robust statistical analysis within this subgroup.

A recent review conducted in China indicates that the prevalence of *H. pylori* is notably higher in the elderly, with rates nearly double those observed in younger individuals 28.0% (95% CI: 23.9-32.5%) in children and adolescents compared to 46.1% (95% CI: 44.5-47.6%) in adults [21]. Considering both *H. pylori* and host-microbe interactions, it is known that this bacterium has coexisted with modern humans for millennia [22]. A study conducted in Brazil also reported an increased *H. pylori* prevalence associated with age, independent of sex [23]. In our study, advanced age was similarly observed as a risk factor for both *H. pylori* Ig A and Ig G positivity, likely due to an increased risk of possible exposure among patients.

The induction of low-grade inflammation due to *H. pylori* has been hypothesized as one of the pathogenic mechanisms underlying various extragastric manifestations of *H. pylori* [24]. Inflammation markers such as ESR and C-reactive protein (CRP) have been shown to correlate with gut microbiota; for instance, a positive correlation exists between Bacteroidetes abundance and CRP/ESR, while a negative correlation is observed between Firmicutes and CRP/ESR [25]. High serum levels of CRP and TNF-α were reported in preeclamptic women who were seropositive for *H. pylori* compared to seronegative subjects [26]. Unfortunately, the existing literature on this subject presents inconsistent and sometimes contradictory findings. A cross-sectional cohort study revealed no interaction between systemic inflammation and *H. pylori*, investigating CRP levels, neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR) to assess systemic inflammation [27]. On the contrary, Sağlam et al. found an increased neutrophil count and PLR in individuals positive for *H. pylori* [28]. In our study, the relationship between elevated ESR and positive *H. pylori* IgA levels was found to be statistically significant.

One review suggests that *H. pylori* infection may alter magnesium levels in patients with renal disease, although the underlying mechanisms remain unconfirmed [29]. Hafizi et al. [30] investigated the association between serum magnesium levels and *H. pylori* in a cross-sectional study involving stable kidney transplant patients. They utilized the urea breath test (UBT) to detect *H. pylori* and found higher magnesium levels in *H. pylori*-positive patients [30]. However, no significant relationship was found between serum *H. pylori*-IgG antibody titers and serum magnesium levels in patients with type 2 diabetes mellitus and chronic kidney disease [31]. Conversely, Öztürk et al. [32] reported significantly lower serum magnesium levels in *H. pylori* positive children compared to healthy controls. Considering all these conflicting data, establishing a clear relationship is challenging; however, in our study, hypomagnesemia was identified as a risk factor for *H. pylori* Ig A positivity. Although the use of proton pump inhibitors (PPIs) has not been studied across the entire cohort, the induction of hypomagnesemia by PPIs is a well-documented phenomenon, and this relationship is dose-dependent [33]. However, our study does not clarify whether hypomagnesemia is associated with PPI, which should be acknowledged as a limitation. Therefore, the observed association between *H. pylori* Ig A and magnesium levels may not be directly related to AS itself. It is possible that *H. pylori*-infected patients are more likely to utilize PPIs, and this likelihood may be even higher among AS patients, given their more frequent use of nonsteroidal anti-inflammatory drugs (NSAIDs).

On the other hand, the greatest genetic predisposition towards AS is known to be associated with the presence of HLA-B27 positivity [34]. The significance of gut microbiota is crucial in the pathogenesis of axSpA [35]. A recent meta-analysis demonstrated a strong association between infections and the development of AS through case-control and cohort studies [8]. Environmental factors may contribute to the disease's manifestation in genetically predisposed individuals, resulting in dysbiosis [36]. Recent studies have also found no correlation between disease activity and *H. pylori* in AS patients. Only 22.2% of patients with active AS were positive for *H. pylori* in stool samples. In our study, there was no significant effect of HLA-B27 positivity or BASDAI on *H. pylori* Ig A and *H. pylori* Ig G positivity.

Strengths and Limitations

We utilized serum *H. pylori* antibody tests, while *H. pylori* stool antigen tests, urea breath test, or invasive tests offer more accurate and quicker detections. The sensitivity and specificity of the *H. pylori* antibody tests are lower. We consider this to be one of the major limitations of the study. Nevertheless, serological tests are widely used and less expensive non-invasive tests for diagnosing *H. pylori* infection. They are more appropriate for population screening than for diagnostic purposes. Relying solely on serological tests to assess *H. pylori* infection status poses limitations, particularly in the absence of confirmatory testing (e.g., urea breath test or stool antigen). The lack of confirmation of infection presence via the aforementioned tests can be considered a weakness of the study. Furthermore, this study represents a single-center experience and includes a relatively small patient population. As this study was based on retrospective data, a causal relationship cannot be established. As previously mentioned, the limited number of patients with hip joint involvement precluded further subgroup analyses within this cohort. In patients with a history of uveitis, those with recurrent episodes and those with a single episode were grouped together, thereby preventing the formation of a homogeneous subgroup. Moreover, the inclusion of only those patients with available *H. pylori* antibody test results in the hospital system introduces a potential selection bias. Additionally, the lack of data regarding PPI use posed a challenge in interpreting serum magnesium levels, as PPIs are known to affect magnesium homeostasis.

One of the main strengths of this study is the use of a well-defined patient group without comorbidities, which reduces confounding and allows a clearer understanding of disease-related associations. The relatively large sample size also increases the reliability of the results. In addition, the use of multivariable logistic regression makes the analysis stronger by identifying independent factors linked to seropositivity in a clear and systematic way.

CONCLUSION

As observed in our study, increased age may be risk factor for exposure to *H. pylori*. Patients with elevated

ESR or hypomagnesemia may be monitored closely for accompanying *H. pylori* infection. The presence of uveitis or hip involvement may serve as predictive indicators for *H. pylori* infection. Understanding the role of *H. pylori* in AS could provide valuable insights into the disease's progression and facilitate the development of more effective treatment strategies. Further investigations with larger patient cohorts are necessary to deepen our understanding of its potential influence on AS pathophysiology.

Ethics Approval and Consent to Participate

This study was approved by the Pamukkale University Non-Interventional Clinical Research Ethics Committeel (Decision No: 2019/20; date: 19.11.2019). All procedures were conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments. Informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data.

Data Availability

All data generated or analyzed during this study are included in this published article. The data that support the findings of this study are available on request from the corresponding author, upon reasonable request.

Authors' Contribution

Study Conception: FV; Study Design: FV; Supervision: FV, VÇ; Funding: FV; Materials: FV; Data Collection and/or Processing: FV; Statistical Analysis and/or Data Interpretation: FV; Literature Review: FV, VÇ; Manuscript Preparation: FV and Critical Review: FV, VÇ.

Conflict of Interest

The author(s) disclosed no conflict of interest during the preparation or publication of this manuscript.

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