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Correlation between Helicobacter Pylori Caga Antibody Serum and Gastric Premalignant Lesions in Helicobacter Pylori Patients

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ABSTRACT

Introduction: Helicobacter pylori (H. pylori) is a spiral-shaped, anaerobic, and gram-negative pathogenic bacteria found in the gastric mucosa that causes chronic gastritis and gastric cancer. One of the most studied H. pylori virulence factors is the CagA protein in which positive anti-CagA antibodies increase the risk of malignancy in the stomach. This research was aimed to determine the correlations between Helicobacter pylori CagA antibody serum and gastric premalignant lesions in Helicobacter pylori patients.

Method: This was a cross-sectional and analytic research. The sample of this study were patients diagnosed with Helicobacter pylori at Haji Adam Malik General Hospital in Medan who corresponded the inclusion criteria. The research was conducted from January to December 2022. The sampling technique used was consecutive sampling. Selected subjects underwent endoscopy and biopsy, as well as antibody detection of CagA, then the data analysis was carried out.

Results: The number of samples that included in this study were 60 people. Based on demographic characteristics, the majority of patients were women, Batak ethnic, having a normal body mass index, not having a history of alcohol consumption, and non-smokers. The majority of people with Helicobacter pylori did not have CagA antibodies. There was a significant relationship (p=0.009) between antibody of CagA and gastric premalignant lesions, as well as the prevalence ratio is 2.6.

Conclusion: There is a correlation between antibody of CagA and gastric premalignant lesions in patients with Helicobacter pylori infection.

Keywords

CagA, Helicobacter pylori, Gastric premalignant lesion

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INTRODUCTION

Helicobacter pylori (H. pylori) is a spiral-shaped, anaerobic and gram-negative pathogenic bacteria found in the gastric mucosa.[1] Changes in bacterial epidemiology have been associated with reductions in peptic ulcer disease and gastric cancer. Syam et al reported a prevalence of H. pylori infection was 22.1% (59/267).[2] Helicobacter pylori infection is now accepted as the main cause of chronic gastritis. Several epidemiological studies have shown that H. pylori infection is also associated with severe gastritis-related diseases, including peptic ulcers and gastric cancer. The prevalence of gastric cancer is approximately 3% in H. pylori-positive patients.[3] The incidence of gastric cancer by age in Indonesia has been reported to be 2.8/100,000, which is low compared to that recorded among other Asian countries. Until March 2013, only 313 hospitals provided gastrointestinal endoscopy services in Indonesia. Although these hospitals are spread across 33 provinces, 72% (98/136) of them are located on Java.Of the several ethnic groups in Indonesia, the highest prevalence of H. pylori is found in Papua, Batak and Bugis ethnicities.[2]

As a pathogenic bacteria, H. pylori can live in an acidic environment, then penetrate the gastric mucosa, and finally colonize the mucosa. These bacteria have several important factors including urease (Ure A-1),

Endotoxin Lipopolysaccharide (LPS), flagellin (fla A, fla B), adhesion (hpa, chapter A1, hopZ, alp A, alp B) and proteins that activate neutrophil activating protein (NAP). All of the above factors were found in all H. pylori strains, whereas factors such as CagA antigen, PAI molecule, vacA/s1, ice-A1 were not found in all H. pylori strains.[4]

The most studied H. pylori virulence factor is cytokine-associated protein A [CagA]. CagA-producing strains have been reported associated with severe clinical outcomes, especially in Western countries. CagA is a highly immunogenic protein with a molecular weight between 120 and 140 KDa. The variation in CagA size is due to the presence of a variable number of repeat sequences located in the 3′ gene region. The repeat region contains the Glu-Pro-Ile-Tyr-Ala (EPIYA) motif. Recently, sequences were annotated using segments (20–50 amino acids) flanking the EPIYA motif (that is, EPIYA-A, -B, -C or -D segments). Recent studies have shown that east Asian-type CagA, which contains an EPIYA-D segment, exhibits a stronger binding affinity for Src homology-2 domain-containing phosphatase (SHP)2 and a greater ability to induce morphological changes in epithelial cells than Western- type CagA, which contains an EPIYA-C segment segment. Another recent study demonstrated that H. pylori strains harboring East Asian-type CagA induced higher amounts of IL-8 from gastric epithelial cells than those harboring Western-type CagA. Therefore, East Asian strains are believed to be more virulent than Western strains, and this may be the reason why the incidence of stomach cancer is relatively higher in East Asian countries than in Europe, North America and Australia. In addition, in Western countries the incidence of gastric cancer is higher in patients infected with strains carrying multiple EPIYA-C repeats compared to those infected with strains with a single repeat.[3]

In 2003, Huang et al. performed a meta-analysis of correlation between CagA seropositivity and gastric cancer. They concluded that CagA-positive strains of H. pylori increase the risk of gastric cancer. The odds ratio (OR) for gastric cancer risk by anti-CagA antibody positive in the fixed model was 1.49. Subjects infected with H. pylori containing the cagA gene did not always induce serum CagA antibodies. For example, although most Japanese H. pylori carry the cagA gene, serum CagA antibodies are detectable in only 43.1–45.5% of infected subjects. This suggests that serum CagA antibodies may be a more useful marker in East Asian countries than the cagA gene.[3]

METHOD

This research was an analytical study using a cross-sectional design that assessed correlation between H. pylori CagA antibody serum and premalignant gastric lesions in H. pylori patients, which was conducted at Adam Malik Haji Center General Hospital in Medan after obtaining Ethical Clearance.

The research sample was patients with a diagnosis of H. pylori who treated at Haji Adam Malik General Hospital who met the inclusion criteria, namely men and women aged > 18 years, dyspepsia patients with positive H. pylori, received information and informed consent with voluntary and written participation; and not included in the exclusion criteria, namely patients who had received H. pylori eradication therapy in the last 6 months or were currently on eradication therapy, consumption of proton pump inhibitors, H2 receptor antagonists for the last 7 days and patients diagnosed with gastric cancer. Total research subjects were 42 people. The sampling technique will be carried out by non-probability sampling, namely by consecutive sampling technique until the minimum size is met.

After recruitment, a Campylobacter-Like Organism Test was carried out to detect H. pylori. Then a histopathological examination was carried out to determine whether there were premalignant gastric lesions. After that, serum CagA antibodies were examined by ELISA

Endoscopy Examination and Biopsy

Endoscopic examination using a scope (Olympus, Tokyo, Japan) was carried out at H. Adam Malik General Hospital in Medan. Endoscopic examination was carried out by experienced endoscopist on each subject examination. Endoscopy was performed after the subject fasted overnight (10-12 hours). Endoscopy was performed to evaluated gastric mucosa which includes edema, erythema (spotted, patchy, linear), exudate,

bleeding, erosive and tissue harvesting for histopathology. Biopsy was performed in five places (A1, A2, A3, C1, C2) namely:

- Major and minor curvature of the distal antrum (A1-A2)
- Angled incisura minor curvature (A3)
- Anterior and posterior walls of the proximal body (C1-C2)
- If there are suspicious findings, such as redness of the mucosa, but not in the places mentioned, a biopsy is also done.

Examination of Campylobacter – Like Organisms

This examination is carried out after a biopsy is performed. Then the gastric tissue was put into a gel medium containing urea and a pH indicator. After incubation, the urease enzyme from Helicobater pylori will break down urea into ammonia and CO2. Ammonia will react with water and cause an alkaline environment. An alkaline environment will change the color of the pH indicator from yellow to magenta

Histopathological Examination

Biopsy specimens were taken during endoscopic examination from five locations and H&E staining was performed for diagnosis of gastritis and gastric premalignant lesions. Histopathological examination was carried out at Department of Anatomical Pathology, Faculty of Medicine, University of North Sumatra, which was carried out by Anatomical Pathology Specialists.

CagA Antibody Test

Preparation of specimens for gel electrophoresis examination, to separate H. pylori from its protein. Then the results of the electrophoresis gel were dripped onto the nitrocellulose membrane. After that, the membrane was incubated with protein solution to prevent free bonding. Then, it will show the positive or negative results.

Statistical Analysis

Data analysis was performed using SPSS version 26. Clinical and demographic data of the subject will be displayed in the form of descriptive tables. Analysis of correlation between CagA H. pylori antibody serum and premalignant lesions was performed using the Chi-square test and alternative Fisher's Exact test if the expected count was less than 5%. It is said to be significant if the p-value <0.05.

RESULT

In this research, based on age, the subject with the oldest age was 68 years old, while the youngest was 19 years old. The mean age of the subjects was 49 years old. Based on gender, the most sample distribution was women as many as 31 people (51.7%). The distribution based on occupation was mostly housewives as many as 27 people (45%) and the least were farmers, civil servants and entrepreneurs, each as many as 1 person (1.7%). Distribution based on recent education was mostly high school as many as 39 people (65%) and the least was elementary school as many as 5 people (8.3%). The distribution based on the majority ethnicity is the Bataknese as many as 37 people (61.7%) and the least is the Minangnese as many as 5 people (8.3%). Distribution based on body mass index, the majority of respondents had normal BMI, namely 20 people (33.3%), while the BMI group that was the least overweight namely 11 people (18.3%). Distribution based on alcohol consumption, the majority of the sample as many as 51 people (85%) do not consume alcohol. Most of the samples did not smoke or were included in light smokers as many as 38 people (63.3%).

Based on Table 2, results of the CagA antibody examination found 29 samples (48.3%) had positive results. As for the presence of gastric premalignant lesions, in this research found 21 people (35%) with gastric premalignant lesions.

Table 1. Distribution of Subjects and Research Frequency Based on Demographic Characteristics

Parameter	Total	Percentage (%)
Age (years old), *Mean*	49,12	
Genders		
Male	29	48,3
Female	31	51,7
Occupation		
Housewife	27	45
Student	4	6,7
Farmer	1	1,7
Civil Servants	1	1,7
Employee	26	43,3
Enterpreneur	1	1,7
Educations Levels		
Elementary School	5	8,3
Junior High School	8	13,3
Senior High School	39	65
University	8	13,3
Ethnicity		
Bataknese	37	61,7
Javanese	12	20
Acehnese	6	10
Minangnese	5	8,3
Body Mass Inedx		
Underweight	13	21,7
Normal	20	33,3
Overweight	11	18,3
Obesity	16	26,7
Alcohol		
Yes	9	15
No	51	85
Smokers		
Moderate-Severe	22	36,7
Non smokers- Mild	38	63,3

Table 2. Distribution of Subjects and Study Frequency Based on Results of CagA Antibodies and Gastric Premalignant Lesion

Parameter	Total	Percentage (%)
CagA Antibodies		
Positive	29	48,3
Negative	31	51,7
Gastric Premalignant Lesion		
Yes	21	35
No	39	65
Total	60	100

Table 3. Crostabulation of CagA Antibodies and Gastric Premalignant Lesions

Variable	Gastric Premalignant Lesions				P value	PR
	Yes		No			
	n	%	n	%		
CagA Antibodies						
Positive	15	71,4	14	35,9	0,009*	2,672
Negative	6	24,6	25	64,1		
Total	21	100	39	100		

*p<0,05

Correlation CagA Antibodies and Presence of Gastric Premalignant Lesions

Table 3 below presents the crosstabulation of CagA antibodies, which were assessed using ELISA examination, and premalignant gastric lesions, which were assessed based on histopathological examination. From table 3, it can be seen that respondents who showed positive CagA antibody results and histopathological results of gastric premalignant lesions were 15 people (71.4%). The prevalence ratio of CagA antibody and gastric premalignant lesions was 2.672 (PR > 1) which means that people with positive CagA antibodies are 2.672 times more likely to have gastric premalignant lesions after Helicobacter pylori infection. The results of the crosstabulation test showed a significance of 0.009. This number is smaller than the significance limit value set, namely 0.05. This leads to rejection of the null hypothesis therefore it is interpreted that CagA antibody has a statistically significant relationship with premalignant gastric lesions in Helicobacter pylori patients.

DISCUSSION

In this research, 60 respondents met the criteria as research subjects and then divided into CagA antibody categories which were assessed using ELISA examination and gastric premalignant lesions which were assessed using histopathological examination.

In this research, the youngest subject was 19 years old and the oldest was 68 years old with an average age of 49 years old. Boreiri et al study showed that there were 7 people in the intervention group aged 40-50 years, 9 people aged 51-60 years, and 24 people aged > 60 years. The analysis showed increase of incidence and mortality rate caused by gastric lesion disorders with increasing age.[5] Similar results were also found in Peleteiro et al study where there was an increased risk of developing premalignant gastric lesions at an older age, namely those aged >50 years.[6]

Based on body mass index category, mean subjects BMI was 22.4435 kg/m2 with the lowest BMI was 15.82 kg/m2 and the highest was 33.59 kg/m2. Based on the BMI classification, the majority of patients had normal BMI, while the cumulative number of overweight and obese patients reached 27 people (45%). Study by Siregar et al showed that there were 12 (22.2%) overweight samples who had gastric premalignant lesions. The results of the analysis showed that overweight BMI did not have a significant relationship with incidence of gastric premalignant lesions.[7]

In this research, there were 37 samples (61.7%) Bataknese, 12 samples (20%) Javanese, 6 samples (10%) Acehnese and 5 samples (8.3%) Minangnese. The majority of samples were Bataknese are in line with and not much different from Siregar et al study which shows that out of 120 people, 67 samples (60.1%) are Bataknese. The analysis of this study showed that there was a significant relationship between ethnicity and the incidence of premalignant gastric lesions which Batak ethnicity increased the risk of gastric premalignant lesions up to 1.69 times.[7]

According to educational characteristics, in this research the majority of the sample had as much as 39 people (65%) graduated from senior high school, while sample graduated from junior high school and university each 8 people (13.3%), and elementary school as many as 5 people (8.3%). Study conducted in 2018 found out of a total 120 samples, 100 people (83.3%) had high education levels and 20 people (16.7%) had low education levels. The results of the analysis showed that there was no relationship between educational level and the incidence of premalignant gastric lesions.[7]

The majority of the samples in this research did not consume alcohol. Only 9 people (15%) consumed alcohol. Peleitro et al found 101 samples (72.7%) in the control group consuming more than 7 glasses of alcohol per week and in the intestinal metaplasia group there were 59 samples (79.7%) consuming more than 7 glasses of alcohol per week. The results of the analysis show that alcohol consumption increase the risk of premalignant gastric lesions, especially abnormalities in intestinal metaplasia.[6] Leung et al stated in their study that there is a relationship between alcohol and gastric precancerous lesions. Based on a study conducted on 435 samples, there were 80 out of 230 (34.8%) samples in the group with gastric precancerous lesions who consumed alcohol and 54 out of 205 (26.3%) samples in the control group who consumed alcohol. The results of the tabulation test stated that there was a relationship between alcohol consumption and gastric precancerous

lesions with a p value = 0.025 and an OR value of 1.61.[8] Similar results were found in Siregar et al study where there was a relationship between alcohol and gastric precancerous lesions (p = 0.017).[7]

The number of samples in this research which were moderate-to-heavy smokers was 22 people (36.7%). You et al showed that in the intervention group there were 149 (56.2%) samples who smoked where 54 of them smoked for less than 25 years and the remaining 85 samples smoked for more than 25 years. The results of the analysis showed an increased risk of gastric premalignant lesions in the heavier smokers group, although it was not statistically significant.[9] Another study in Venezuela stated that smoking was a significant predictor of gastric premalignant lesions. Compared to people who have never smoked or have ever smoked, smoking significantly increases the risk of dysplasia by 2.14 times and intestinal metaplasia by 1.33 times. People who smoke more than 10 cigarettes per day will increase the risk of dysplasia by 3.58 times and intestinal metaplasia by 1.77 times.[10]

CagA antibody examination found 29 samples (48.3%) had positive results. Peleteiro et al study showed that in the control group there were 68 samples (46.3%) had positive results on CagA antibody examination, while in the intestinal metaplasia group there were 63 samples (78.8%) had positive results on CagA antibody examination.[6] In the category of gastric premalignant lesions, there were 21 people (35%) who showed histopathological results of gastric premalignant lesions. A study conducted in 2009 showed that 80 samples had gastric precancerous lesions with details, 34 samples had non-atrophic gastritis, 14 samples had multifocal gastritis, 29 samples had intestinal metaplasia, and 2 samples had dysplasia.[11]

Correlation of CagA Antibodies and Gastric Premalignant Lesions

In this research, crosstabulation test results using Pearson Chi-Square test found a p value of 0.009. This result is smaller than the significance limit value set, namely 0.5. This leads to rejection of the null hypothesis therefore it can be concluded that CagA antibody has a statistically significant relationship with gastric premalignant lesions in Helicobacter pylori infection.

A study conducted by Yakut et al in 2013 showed results that were in line with this research. The study was conducted on 98 patients who were positively infected with Helicobacter pylori, 38 of 98 patients divided into 4 groups showed positive results for CagA antibody. Group I is the sample group with H.pylori positive chronic non-atrophic gastritis, Group II is the sample group with Chronic atrophic gastritis, Group III is the sample group with Intestinal metaplasia, and Group IV is the sample group with Dysplasia. Number of patients positive for CagA antibody in groups I-IV respectively was 7, 9, 8, and 14. Statistical test results showed that CagA antibody was related to group II (p = 0.09), group III (p = 0.006), and group IV (p < 0.001) when compared to group I. Yakut el showed sensitivity and specificity of CagA antibody in group II was 52.9% and 64.1%, group III was 38% and 61%, and group IV was 63.6% and 68.4%.[12]

Another study in 2007 showed similar results. This study conducted on 223 patients showed that CagA antibodies were associated with precancerous gastric lesions with a p value <0.001 in the atrophic gastritis, corpus atrophic gastritis, and intestinal metaplasia groups. In these 3 groups, CagA antibody showed a fairly high sensitivity (82.8% ; 90.3% ; 95.7%) although it had a low specificity (51.5% ; 47.9% ; 47%). High sensitivity but low specificity coupled with more than 70% of individuals with Helicobacter pylori infection showing positive CagA antibody results means that this marker cannot be used as the sole marker in screening for the detection of mass gastric premalignant lesions in the Costa Rican population where the study was conducted. The combination with the VL-PG marker showed a good accuracy with a sensitivity of 77.4% and a specificity of 80.7%.[13]

Similar research was also conducted in three Latin American countries, namely Mexico, Colombia, and Paraguay. The results showed CagA antibodies also had a significant relationship with the incidence of gastric premalignant lesions. In addition, the OR value in each country was above 1, namely 2.1 (Mexico), 3.0 (Colombia), and 3.1 (Paraguay), which indicated that positive CagA antibodies would increase gastric premalignant lesions. Therefore, this study suggests using CagA antibody as a biomarker against gastric premalignant lesions.[14]

Peleteiro et al. conducted a study with risk analysis such as alcohol consumption and smoking, as well as several antibody markers such as VacA and CagA with the incidence of gastric premalignant lesions, which in this study focused on the type of intestinal metaplastic lesions. The results of this study showed that 78.8% of patients with intestinal metaplasia had CagA antibodies. The OR value of positive CagA antibodies with premalignant gastric lesions is also above 1, which is 4.70.[6]

Research conducted by Pan et al in 2013 showed results that were in line. This study conducted in a Chinese population demonstrated that CagA antibody response was identified as an independent predictor of gastric premalignant lesions evolution which found CagA seropositive as much as 83.9%. In this study it was found that there was a significantly increased risk of chronic atrophic gastritis (OR = 6.73, 95% CI = 2.96–15.28), intestinal metaplasia (OR = 2.57, 95% CI = 1.45–4.55) or dysplasia (OR = 2.29, 95% CI = 1.05–5.01) in subjects with positive anti-CagA antibodies.[15]

A 2007 study conducted by Plummer et al showed similar results. This study demonstrated a very strong association between current infection with CagA-positive H. pylori strains and the severity of gastric premalignant lesions in a Latin American population correlated with H. pylori infection and gastric cancer. The prevalence of cagA-positive H. pylori infection is 75% in subjects with type III intestinal metaplasia or dysplasia compared with 17% in subjects with normal gastric mucosa.[16]

Another study conducted in Korea also showed similar results where among subjects infected with Helicobacter pylori, less than 10 percent were infected with a CagA-negative strain. In this study it was also found that CagA seropositivity was significantly associated with the risk of gastric cancer among subjects infected with Helicobacter pylori (OR=3.74, 95% CI 1.10–12.73), and significant interaction was found between Helicobacter pylori and CagA.[17]

There are other studies that show different results from this study. Research conducted on 128 samples showed that there was no association between CagA antibody and gastric premalignant lesions. In that study, out of 40 samples with gastric pre-malignant lesions, 23 samples showed an increase in CagA antibodies above normal whereas crosstabulation test results found a p-value of 0.2. The study presented that markers associated with gastric premalignant lesions were PGI and PG I/II ratio.[18]

CONCLUSION

There is a correlation between CagA antibodies and gastric premalignant lesions in patients with Helicobacter pylori infection. Patients with Helicobacter pylori infection are more dominantly found female sex, batak ethnicity, patients with a normal body mass index, patients without history of alcohol consumption, and patients who are non-smokers or light smokers.

DECLARATIONS

Ethics approval and consent to participate. Permission for this study was obtained from the Ethics Committee of Universitas Sumatera Utara and Haji Adam Malik General Hospital.

CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

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The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTIONS

All authors significantly contribute to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. Contribute to drafting, revising, or critically reviewing the article. Approved the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of the work.

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