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Correlation Between Helicobacter Pylori VacA Antibody Serum and Gastric Premalignant Lesions in Helicobacter Pylori Patients

Ridho Firmansyah Sitorus[1]*

[1] *Department of Internal Medicine, Faculty of Medicine, University of North Sumatra, H. Adam Malik General Hospital Medan*

***Corresponding Author**: Ridho Firmansyah Sitorus, E-mail: srirahmaniaamini14@gmail.com

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ABSTRACT

Introduction: Helicobacter pylori (H. pylori) is a gram-negative bacteria that colonizes in human digestive tract that can cause various problems in the stomach. The virulence factors involved in this process consist vacuolating cytotoxin gene A (vacA) which can be used as a marker of the progressivity of H.pylori infection to Atrophic Gastritis and Intestinal Metaplasia. This research was aimed to determine the correlations between Helicobacter pylori vacA 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 VacA, then the data analysis was carried out.

Results: Demographic characteristics of H. pylori patients show that mean aged was 49 years and the majority patients are female (51.7%), bataknese (61.7%) with normal mean body mass index (22.4435 kg/m2), not consuming alcohol (85%), and nonsmokers or mild smokers (63.3%). Pearson chi-square test results didn't found significant correlations (p=0.639) between VacA antibody and gastric premalignant lesions.

Conclusion: There was no significant correlation between VacA antibody and gastric premalignant lesions.

Keywords

VacA, Helicobacter pylori, gastric premalignant lesion

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INTRODUCTION

Helicobacter pylori (H. pylori) is a gram-negative bacteria that colonizes in human digestive tract. H. pylori is a spiral-shaped, gram-negative bacteria that has 7 flagella with a cytoplasm containing nucleoid material and ribosomes. H. pylori infection affects nearly half of the population worldwide. In developing countries, the prevalence of this infection is 90%.[1,2]

Helicobacter pylori infection can lead to chronic infection and H. pylori carriers can cause various problems in the stomach. In most individuals infected with H. pylori, 10% of the population has peptic ulcer, 1 to 3% has gastric adenocarcinoma, and 0.1% has mucosa-associated lymphoid tissue (MALT) lymphoma. Research by Uemura et al. states that gastric cancer occurs in 3% of population with H.pylori infection.[3,4] The 5-year survival rate for gastric cancer in worldwide is around 31%, while the survival rate for pre-metastatic lesions is 67%. The Asian population has a better prognosis than the rest of the population.[5]

Helicobacter pylori has virulence factors involved in this process, strains harboring variants of vacuolating cytotoxin gene A (vacA) and cytotoxin associated gene A (cagA) which can induce an increased

inflammatory response in infected cells that can alter the gastric mucosa to cause gastric malignancy. which starts from pre-malignant lesions, namely atrophic gastritis and intestinal metaplasia in gastric cells.[6]

Cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A gene (VacA) are associated with increased H.pylori pathogenicity. Research by Suraini et al. found that 73.91% of gastric cancer patients were seropositive for H.pylori CagA and VacA. Examination of VacA H.pylori antibodies can confirm a history of H.pylori infection in patients with gastric malignancy. According to research conducted by Mohamed Reda Jouimyi, et al in 2021, they found that identification of VacA antibodies could be a marker that H.pylori infection could develop into Atrophic Gastritis and Intestinal Metaplasia.[7]

METHOD

This research was an analytical study using a cross-sectional design that assessed correlation between H. pylori VacA 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 56 people. The sampling technique will be carried out by non-probability sampling, namely by consecutive sampling technique until the minimum size is met.

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.

VacA 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 VacA 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

The population with a diagnosis of H. pylori at Haji Adam Malik General Hospital during research period was 93 people. 18 people had received H. pylori eradication therapy in the past 6 months or were on the usual antibiotic therapy used in eradication therapy, 14 people took proton pump inhibitors or H2 receptor antagonists for the last 7 days, and 1 person was diagnosed with gastric cancer, therefore there were 60 respondents who met the criteria as research subjects. This number exceeds the minimum sample requirement in accordance with the calculation of the minimum number of samples required in the research methods section with a total of 28 samples. The following is a description of the research subjects on several parameters.

Table 1. Description of research subjects

Parameter	n	Minimum	Maximum	Mean
Age	60	19	68	49,1167
BMI	60	15,82	33,59	22,4435
Parameter		Total		Percentage (%)
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
Parameter		Jumlah		Persentase (%)
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
Alcohol				
Yes		9		15
No		51		85
Smokers				
Moderate-Severe		22		36,7
Non smokers- Mild		38		63,3
Total		60		100

In this research, based on age, the oldest age of research subjects was 68 years old and the youngest was 19 years old with mean research subjects age was 49 years old. Descriptive analysis showed that the highest body mass index in this research was 33.59 kg/m^2 and the lowest was 15.82 kg/m^2 with mean body mass index of 60 samples was 22.4435 kg/m^2.

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

Parameter	Total	Percentage (%)
VacA Antibodies		
Positive	45	75
Negative	15	25
Gastric Premalignant Lesion		
Yes	21	35
No	39	65
Total	60	100

Univariate analysis of 60 samples was carried out with results based on gender was mostly women as many as 31 people (51.7%), based on work mostly housewives as many as 27 people (45%) followed by employee as many as 26 people (43.3%)) and the least were farmers, civil servants, and entrepreneurs with each 1 person (1.7%). Based on their last education, 39 people (65%) graduated from senior high school then 8 (13.3%), 8 (13.3%) and 5 (8.3%) samples respectively graduated from junior high school, university and elementary school. The majority ethnicity was bataknese as many as 37 people (61.7%) and the least was minangnese as many as 5 people (8.3%). Based on alcohol consumption, 51 people (85%) did not consume alcohol. Most of the samples did not smoke or were included in mild smokers as many as 38 people (63.3%). The results of the VacA antibody examination, 45 samples (75%) showed positive results and based on the findings of gastric premalignant lesions, 21 people found gastric premalignant lesions.

Table 3. Crostabulation of VacA antibodies with premalignant gastric lesions

Variable	Premalignant gastric lesions				P value	PR
	Yes		No			
	n	%	n	%		
VacA Antibodies						
Positive	15	71,4	30	76,9	0,639	0,8333
Negative	6	28,6	9	23,1		
Total	21		39			

Table 3 shows respondents with positive VacA antibody results and histopathological results of gastric premalignant lesions as many as 15 people (71.4%). The prevalence ratio of VacA antibodies to gastric premalignant lesions was 0.8333 (PR < 1) which was interpreted as H. pylori infection patient with positive VacA antibodies 0.8333 times more likely to have gastric premalignant lesions. The results of the Pearson chi-square crosstabulation test showed a significance value of 0.639. This figure is smaller than the significance limit value which is set at 0.05 which leads to the rejection of null hypothesis therefore it is interpreted that the VacA antibody is not statistically significantly related to gastric premalignant lesions in H. pylori infection patients.

DISCUSSION

In this research, 60 respondents met the criteria as research subjects. This number corresponds to the amount required for data significance according to research methods section calculations. The sample of this research was divided into vacA antibodies categories which were assessed using ELISA examination and gastric premalignant lesions categories which were assessed using histopathological examination.

In this research, the youngest subject was 19 years old and the oldest was 68 years old with mean age of 49 years old. A study assessed prevalence of premalignant gastric lesions showed that mean sample age was

not much different from this research, namely 53.1 years old, with the youngest sample age was 17 years old and the oldest was 86 years old. Others study found mean age was 53 years old with a sample age range of 35-85 years.[9]

Based on body mass index, the mean BMI of subjects of this research was 22.4435 kg/m2 with the lowest BMI was 15.82 kg/m2 and the highest was 22.39 kg/m2. Other studies have shown majority mean BMI of subjects was normoweight, similar to this study, although there are samples with BMI reaching above 40 kg/m2. The majority of research sampels did not consume alcohol. Only 9 people (15%) consumed alcohol. Hoed et al's research showed that of 369 samples, 39% of them did not consume alcohol, 48% drank 0-2 glasses of alcohol per day, 11% drank 3-5 glasses of alcohol per day, and the remaining 2.4% drank more than 5 glasses per day. The number of research sampels whose moderate-to-heavy smokers was 22 people (36.7%). One study presented results with slightly different sample characteristics that out of 367 samples, 51% were non-smokers, 25% were smokers, and the remaining 24% were smokers in the past, although there is no data on the number of cigarettes smoked per day.[8]

Based on VacA Antibody examination, there were 45 samples (75%) which showed positive results. This result is higher than a study in 2014 which showed positive results for VacA antibodies was 61 of 118 (52%) samples with positively infected H. pylori.[10]

Based on gastric premalignant lesions, there were 21 people (35%) who showed histopathological results of gastric premalignant lesions. These results were much higher than Hoed et al study which showed findings of gastric premalignant lesions in 34 people (9.3%) of 383 samples.8 It was different from this research where the percentage of gastric premalignant lesion findings reached 35% of total study sample.

A study conducted by Liu et al was conducted to assessed correlation between alcohol consumption and gastric precancerous lesions and found correlation between alcohol and gastric premalignant lesions. However, another study in 2011 showed different results where there was no correlation between alcohol consumption and gastric premalignant lesions (p value 0.14).[8]

A study was conducted to examine the correlation between smoking and gastric premalignant lesions. In that study, the samples that experienced intestinal metaplasia and smoked were 34 people (37.8%). Statistical test results ddin't found correlation between smoking and gastric premalignant lesions (p value 0.9). However, this study found correlation between smoking and gastric cancer (p value 0.01).[11]

Another study showed similar results where the analysis results of 34 people who had premalignant lesions, showed that there was no correlation between smoking and gastric premalignant lesions. Liu et al presented similar results which found correlation between smoking and gastric premalignant lesions (p value 0.043).[8,9]

Research by Siregar et al on 87 samples showed that 43.5% of Batak ethnicity experienced gastric premalignant lesions and 14.6% of non Batak ethnicity experienced gastric premalignant lesions. The results of this study crosstabulation test showed a correlation between Batak ethnicity and gastric premalignant lesions with an OR of 2.97 and a p value of 0.016.[12]

The highest level of education in this research was senior high school as much as 39 people (65%). Another study showed that 36.8% of samples with low education levels had premalignant gastric lesions, while 27.9% had high education levels. The study showed an OR of 1.32 and a p-value of 0.454, which means that there is no relationship between education level and gastric pre-malignant lesions.[12]

In this study, the mean sample age was 49 years old. A study by Kim et al showed that gastric premalignant lesions were most common in group of patients aged 50-59 years (28.7%). The study showed that there was no relationship between age and gastric premalignant lesions (p value 0.547).[13]

The mean body mass index of this research samples was 22.4 kg/m2. A study conducted on 142,832 samples showed that group with highest incidence of intestinal metaplasia per year was the group with BMI > 23-24.9 ; 25-29.9; 30 kg/m2 with successive incidence rates of 6 ; 6,5 ; 7.4 per 1,000 people annually with a HR of 1.04 ; 1.09 ; 1.48 with a p value of 0.001 which indicates a relationship between body mass index and

gastric premalignant lesions. In this study, 48.3% of the sample was male. One study showed that gender was not associated with premalignant gastric lesions.[14]

In this research, the results of the crosstabulation test using Pearson Chi-Square test found a p value of 0.639. This result is smaller than the significance limit value which is set at 0.5 which leads to the rejection of null hypothesis therefore it is interpreted that the VacA antibody is not statistically significantly related to gastric premalignant lesions in H. pylori infection patients. Research by Pan et al in 2014 showed consistent results where there was no significant correlation between VacA antibodies and gastric premalignant lesions (p value 0.220). This study conducted in a Chinese population demonstrated that the VacA antibody response was identified as an independent predictor of gastric premalignant lesions evolution. Whereas in this study found VacA seropositive as much as 38.9%. In this study it was found that there was a significantly increased risk of chronic gastritis (OR = 3.23, 95% CI = 1.90–5.51), intestinal metaplasia (OR = 1.54, 95% CI = 0.93-2.55) or dysplasia (OR = 1.54, 95 % CI = 0.78–3.04) in subjects with positive anti-VacA antibodies.[15]

These results are inconsistent with a 2014 study that evaluated correlation between VacA antibodies and premalignant cancerous lesions. In that study, VacA antibodies were found in 47% of chronic gastritis samples but were also found in 43% of intestinal metaplasia samples. Multiple logistic regression analysis showed that there was an correlation between VacA antibodies and chronic gastritis and intestinal metaplasia (p values 0.005 and 0.01).[16]

Ayala et al study also showed different results. In a study of 347 patients, 90 samples with intestinal metaplasia, 60 with chronic gastritis, 52 with duodenal ulcer, and 145 with non-atopic gastritis. It was found that VacA was associated with premalignant gastric lesions (p value 0.002) and gastric cancer (p value 0.001), but not associated with duodenal ulcers (p value 0.370).[11]

Likewise, in a 2009 study conducted by Douraghi et al shown that there was a significant correlation between VacA antibodies and premalignant gastric lesions which was clearly seen from the results of histopathological changes found in patients with intestinal metaplasia (p value 0.017) and dysplasia (p value 0.032).[17]

A study conducted by Nguyen et al in 2010 showed that there was a correlation between VacA m and 100 patients included 24 peptic ulcer patients and 76 chronic gastritis patients (p value <0.05) while VacA s and VacA I not significantly correlated (p value > 0.05).[18]

Another study in 2016 conducted by Liu et al with different results from this research found a significant association between VacA antibodies and an increased risk of gastric ulcers (OR = 1.64, 95% CI = 1.02–2.62, p value <0.001).[19] Research by Bartpho et al in 2020 showed different results. Based on a study conducted on 166 samples with detailed results of gastric mucosal pathology, the samples showed chronic outcomes in 44 people, premalignant lesions in 52 people, and gastric cancer in 52 people. Samples with positive VacA antibodies in the chronic group were 32 people (73%), premalignant lesions were 14 people (27%), and gastric cancer were 42 people (60%). This results showed a significant correlation between VacA antibodies and gastric premalignant lesions (OR = 2.14, 95% CI = 1.62-4.46, p value 0.036) and gastric cancer (OR = 1.23, 95% CI = 1.13-3.32, p value 0.033).[20]

The results of this research are different from Jouimyi et al study. In this study, which was conducted on 210 samples with histopathological results, 61% of the samples had chronic gastritis, 25% had atrophic gastritis, and 13% had intestinal metaplasia. The VacA s1 antibody genotype increased in 41% of chronic gastritis samples, 57% of atrophic gastritis samples, and 64% of intestinal metaplasia samples. In addition, the VacA s2 antibody genotype also increased in 59% of chronic gastritis samples, 57% of atrophic gastritis samples, and 64% of intestinal metaplasia samples with a p value of 0.03 which was interpreted as VacA antibody genotype was significantly correlated with gastric premalignant lesions.

The study by El Khadir et al also showed different results. Based on the multivariate analysis performed on 248 samples, it was shown that in the intestinal metaplasia sample group there was correlation between the VacAi antibody genotype and intestinal metaplasia (OR = 2.75, 95% CI = 1.59-4.73, p value 0.001) and gastric cancer (OR = 2.68, 95% CI = 1.17-6.13), p value 0.01).[22]

The results of this research not found correlations between VacA antibody and gastric premalignant lesions. This difference may be due to the fact that in this research it was only conducted to detect VacA antibodies without genotyping for VacA S/i/m region strain. Where from several literature journals it was found that the s1/m1 region was most associated with gastric premalignant lesions, while other regional strains were not so associated with gastric premalignant lesions.

The limitations in this study was there was no classification regarding the type of premalignant gastric lesions that occurred in the sample. The VacA test can only detect antibodies without checking VacA strain region. In addition, there are several factors that can influence the occurrence of premalignant gastric lesions but were not found in this research such as a family history of malignancy and prolonged used of NSAID drugs.

CONCLUSION

VacA antibodies were not found to be associated with premalignant gastric lesions. However, it was found that majority of H. pylori patients were female and bataknese with normal body mass index.

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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REFERENCE

1. Garza-González E, Perez-Perez GI, Maldonado-Garza HJ, Bosques-Padilla FJ. A review of Helicobacter pylori diagnosis, treatment, and methods to detect eradication. World J Gastroenterol WJG. 2014; 20 (6): 1438–49.
2. Mc CK. Helicobacter pylori infection. The New England of Journal Medicine. August 2010.
3. Danesh J. Helicobacter pylori infection and gastric cancer: systematic review of the epidemiological studies. Aliment Pharmacol Ther. 1999; 13 (7): 851–6
4. Ari SF. Risk Factors and Prevalence of Helicobacter pylori in Five Largest Islands of Indonesia: A Preliminary Study. PLoS ONE. 2015

5. Miftahussurur M, Shiota S, Suzuki R, Matsuda M, Uchida T. Identification of Helicobacter pylori infection in symptomatic patients in Surabaya, Indonesia, using five diagnostic tests. Epidemiol Infect. 2015; 143: 986–996.
6. Bravo Denisse. Helicobacter Pylori In Human Health And Disease: Mechanisms For Local Gastric And Systemic Effects. World Journal of Gastroenterology. 2016
7. Mohamed JR, Ghizlane B, Imane E. Association of Helicobacter pylori vacA polymorphisms with the risk of gastric precancerous lesions in a Moroccan population. J Infect Dev Ctries. 2021
8. den Hoed CM, van Eijck BC, Capelle LG, van Dekken H, Biermann K, Siersema PD, et al. The prevalence of premalignant gastric lesions in asymptomatic patients: predicting the future incidence of gastric cancer. Eur J Cancer. 2011; 47 (8): 1211-8. DOI: https://doi.org/10.1016/j.ejca.2010.12.012.
9. Liu J, Sun L, Gong Y, Yuan Y. Risk factors of precancerous gastric lesions in a population at high risk of gastric cancer. Chinese Journal of Cancer Research. 2010; 22 (4): 267-273.
10. Siregar J, Darmadi D, Ganie RA. Association Between Serum Midkine Level and Gastric Precancerous Lesion in Patients with Gastritis. Medical archives (Sarajevo, Bosnia and Herzegovina). 2022; 76 (5): 368-372. DOI: https://doi.org/10.5455/medarh.2022.76.368-372
11. Ayala G, Flores-Luna L, Hernández-Amaro D. Association of circulating VacA-neutralizing antibodies with gastric cancer and duodenal ulcer. Cancer Causes Control. 2011; 22: 1425-1434. DOI: https://doi.org/10.1007/s10552-011-9817-5
12. Siregar GA, Parwati I, Achmad TH, Syukriani YF. Association between VEGF-634G>C Gene Polymorphism with Gastric Premalignant Lesions and Serum VEGF Levels in Helicobacter pylori Gastritis Patients. Open Access Maced J Med Sci. 2018; 6 (8): 1328-1334. DOI: https://doi.org/10.3889/oamjms.2018.266.
13. Kim N, Park YS, Cho SI, Lee HS, Choe G, Kim IW. et al. Prevalence and risk factors of atrophic gastritis and intestinal metaplasia in a Korean population without significant gastroduodenal disease. Helicobacter. 2008; 13 (4): 245-55. DOI: https://doi.org/10.1111/j.1523-5378.2008.00604.x
14. Kim K, Chang Y, Ahn J, Yang HJ, Jung JY, Kim S. Body Mass Index and Risk of Intestinal Metaplasia: A Cohort Study. Cancer Epidemiol Biomarkers. 2019; 28 (4): 789–797. DOI: https://doi.org/10.1158/1055-9965.EPI-18-0733
15. Pan KF, Formichella L, Zhang L, Zhang Y, Ma JL, Li ZX. et al. Helicobacter pylori antibody responses and evolution of precancerous gastric lesions in a Chinese population. International journal of cancer. 2014; 134 (9): 2118–2125. DOI: https://doi.org/10.1002/ijc.28560
16. Ki MR, Hwang M, Kim AY, Lee EM, Lee EJ, Lee MM. et al. Role of vacuolating cytotoxin VacA and cytotoxin-associated antigen CagA of Helicobacter pylori in the progression of gastric cancer. Molecular and Cellular Biochemistry. 2014; 396 (1-2): 23–32. DOI: https://doi.org/10.1007/s11010-014-2138-8
17. Douraghi M, Talebkhan Y, Zeraati H, Ebrahimzadeh F, Nahvijoo A, Morakabati A. et al. Multiple gene status in Helicobacter pylori strains and risk of gastric cancer development. Digestion. 2009; 80 (3): 200-207. DOI: https://doi.org/10.1159/000229774
18. Nguyen TL, Uchida T, Tsukamoto Y, Trinh DT, Ta L, Mai BH. et al. Helicobacter pylori infection and gastroduodenal diseases in Vietnam: a cross-sectional, hospital-based study. BMC gastroenterology. 2010; 10: 114. DOI: https://doi.org/10.1186/1471-230X-10-114
19. Li Q, Liu J, Gong Y, Yuan Y. Serum VacA antibody is associated with risks of peptic ulcer and gastric cancer: A meta-analysis. Microbial pathogenesis. 2016; 99: 220–228.
20. Bartpho TS, Wattanawongdon W, Tongtawee T, Paoin C, Kangwantas K, Dechsukhum C. Precancerous Gastric Lesions with Helicobacter pylori vacA+/babA2+/oipA+ Genotype Increase the Risk of Gastric Cancer. Biomed Res Int. 2020; 18: 7243029. DOI: 10.1155/2020/7243029
21. Jouimyi MR, Bounder G, Essaidi I, Boura H, Badre W, Benomar H. et al. Association of Helicobacter pylori vacA polymorphisms with the risk of gastric precancerous lesions in a Moroccan population. J Infect Dev Ctries. 2021; 15: 1124-1132. DOI: 10.3855/jidc.14435

22. El Khadir M, Boukhris Alaoui S, Benajah DA, Ibrahimi SA, Chbani L, El Abkari M. et al. VacA genotypes and cagA-EPIYA-C motifs of Helicobacter pylori and gastric histopathological lesions. Int J Cancer. 2020; 147 (11): 3206-3214. DOI: 10.1002/ijc.33158.