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Association of *Helicobacter pylori* genotype and the clinical outcomes among adult patients who underwent esophagogastroduodenoscopy: A single center study*

Yusi, JAL

Bondoc, EM

Institute of Digestive and Liver Diseases
St. Luke's Medical Center
E. Rodriguez Ave, Quezon City 1112,
Philippines

Correspondence:
Yusi, Jan Axel L., M.D.
axel.yusi@yahoo.com

Abstract

Introduction: Background: Local studies describing the presence of different genotypes of *H. pylori* and their associations with different outcomes are currently not available in the Philippines. Published data show that cagA gene and vacA s1a/m1 gene positivity are associated with greater disease activity and pose a higher risk for gastric cancer development. This study aims to determine the different *H. pylori* genotypes present among infected individuals and its relationship with the different outcomes such as histologic changes, treatment response, and antibiotic sensitivity.
Methods: This was an analytical cross-sectional study that included subjects who underwent gastroscopy from the year 2017 to 2019 and whose data were recorded in a registry. Data on histopathologic findings, genotype identification, antibiotic sensitivity testing and test for *H. pylori* eradication were also collected. Fisher's Exact test was used to test for association.
Results: A total of 110 subjects were included in this study. Fifty-nine percent were female and 55% were within the age range of 40 to 59. The cagA positivity rate was 43%. Fifty-two percent (n=48/92) were vacA positive with s1a/m2 as the major subunit present (31%). Forty-one percent of the subjects had moderate inflammation and 23% had intestinal metaplasia. Fifty-three subjects had data on treatment response with 87% cure rate. Among patients with data on antibiotic sensitivity, 48%, 57%, 4%, and 22% had resistance to metronidazole, levofloxacin, tetracycline, and clarithromycin, respectively. No resistance to amoxicillin was observed. Positive cagA was associated with intestinal metaplasia and moderate inflammation (p=0.001). Positive vacA gene was also associated with moderate inflammation (p=0.001); however, no association was seen when analyzed according to vacA subunits. When analyzed according to cagA+/vacA+ combination, cagA alone, vacA alone, and subjects who were negative for both genes, and histologic findings, there were associations seen with cagA/vacA negative and mild inflammation, vacA alone and moderate inflammation, and cagA+ / vacA+ combination and intestinal metaplasia (p=0.008). No association was seen between different genotypes, treatment response or antibiotic sensitivity.
Conclusion: *H. pylori* infection with positive cagA gene or vacA gene had active, moderate inflammatory changes. Presence of cagA gene alone or in combination with vacA gene were associated with intestinal metaplasia.

Keywords: H. pylori, Helicobacter pylori, cagA, vacA, *H. pylori* genotypes, *H. pylori* genotypes and mucosal changes, Philippine *H. pylori* genotype, *H. pylori* genotypes and antibiotic sensitivity, *H. pylori* genotypes and treatment outcome

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Introduction

Since the discovery of *Helicobacter pylori* by Warren and Marshall, this organism has been described and studied extensively. *H. pylori* is a ubiquitous organism, and it colonizes the stomach in almost 50% of the world population. More than 80% of the adult population in developing countries are suffering from this infection, not to mention the more than 30% of adults infected in developed countries.[1,6] According to a study by Sollano et al., among dyspeptic patients with unremarkable upper gastrointestinal endoscopic findings, *H. pylori* prevalence ranges from 26.5%-79.9%.[32] This infection is a major risk factor for a number of diseases, from benign conditions to the more severe illnesses, which include peptic ulcer disease, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric adenocarcinoma.[1,5]

Gastric cancer is the third leading cause of cancer mortality worldwide. Although its incidence is declining by 1.5% per year in the last decade, it is the 5th most common type of cancer in 2020.[4,5] In the Philippines, not much literature is available on gastric adenocarcinoma, including the burden of the disease. A recent publication mentioned that there is a steady decline in the incidence of gastric adenocarcinoma over the past few decades.[1] There was a decline in incidence from 11.8% to 7.5% seen in Metro Manila and Rizal Province from 1980 to 2002.[2] As mentioned by Quebral et al., improved food preservation practices from salting and smoking to refrigeration can partially explain this decline.[1] Further, apart from dietary factors, there are other contributors to the development of gastric adenocarcinoma among *H. pylori* infected patients. They mentioned that studies analyzing socio-demographic factors and the organism's genetic characteristics are needed to better define and explain these recent trends.

The link between *H. pylori* infection and gastric adenocarcinoma is well studied, and this infection is one of the preventable and treatable causes of cancer. The virulence of *H. pylori* can be categorized according to its ability to colonize, to escape immune response and to induce disease. Examples of the factors that help the organism colonize the stomach area are presence of urease and flagella. Factors that help the organism both escape the immune response and induce disease are the Vacuolating associated cytotoxin A (VacA) and the Cytotoxin associated gene A (CagA) proteins. These proteins are produced by the vacA and cagA genes, respectively.

The cagA encodes for the CagA protein. This protein is one of the key factors that allows the interaction between the organism and the gastric epithelium. The cagA gene is a part of the *cag* pathogenicity island or cagPAI. The cagPAI is also a Type 4 secretory apparatus that serves to deliver the CagA protein into the cell. [6,7,24] CagA is considered an oncoprotein, and it interferes with host cell signaling pathways, and produces severe inflammation and tissue damage. Specifically, it alters the intracellular signal transduction pathways that can lead to malignant transformation.[6] Vacuolating cytotoxin gene A (vacA) encodes for the vacuolating cytotoxin A (VacA). This cytotoxin gives the organism the ability to form vacuole leading to apoptosis of cells in the gastric epithelium. The vacA genetic structure has alleles of the mosaic structure, including the signal (s) and middle (m) regions. The "s" and "m" regions are divided into s1 or s2 and m1 or m2 subtypes, respectively.[6] Combinations of these subtypes will determine the vacuolating activity of the organism. The combination with the highest activity is the s1m1 combination. Between the two subunits, the s1 is noted to be associated with more severe clinical outcomes such as peptic ulcer disease and a more severe inflammatory activity.[6,25] The s1 subunit containing strains of *H. pylori* also have the cagPAI, hence making the disease activity in these patients more active, as shown in some in-vitro studies.[26] In contrast, the s2 subunit containing strains have no cagPAI and does not exhibit vacuole formation. Hence, these infections are associated with less severe outcomes. The vacA m1 strains have been associated with more significant gastric epithelial damage than m2 strains. The study by Atherton reveals a significant association between the strains carrying the vacA m1 alleles and intestinal metaplasia in addition to gastric cancer.[12]

Local studies describing the presence of different genotypes and their associations with different clinical outcomes were not available in the Philippines. Four foreign studies investigating the relationship of *H. pylori* genotype and degree of histopathologic changes such as presence of gastritis, ulceration, metaplasia, dysplasia and neoplasia were

identified. The available studies, however, showed conflicting results. The studies of Atherton, Rosero and Saribasak revealed that vacA positivity was associated with peptic ulcer disease and gastric cancer. In contrast, the study of Hu showed no relationship between these variables.[12,13,14] Regarding data on cagA positivity, only the study by Saribasak showed a positive relationship to peptic ulceration. Two single center studies were identified investigating the influence of *H. pylori* genotype and efficacy of eradication therapy with conflicting results. The article of Zhang investigated the presence of cagA, vacA and iceA, and their relationship to the efficacy of *H. pylori* triple therapy.[11] The study revealed that the genotypes did not affect the effectiveness of the treatment regimen. On the other hand, the study done by Zhao showed that cagA positivity was a predictor of successful eradication. Thus, this study aimed to provide additional data that may possibly help in elucidating these dilemmas.[39]

The aim of this study was to determine the *H. pylori* genotypes present among infected individuals and its association to clinical outcomes. This was a single center analytical cross-sectional study involving patients who had *H. pylori* infection. The study determined if the specific genotype of the organism was associated with histologic changes, response to treatment, and antibiotic resistance.

Methods

Type of Study, Time Period and Target Population

This was an analytical cross-sectional study, conducted from May 2023 to April 2024. Subjects enrolled in the study by Lucentales et al.,[30] who had esophagogastroduodenoscopy (EGD) and were diagnosed with *H*. *pylori* infection were included. Demographic characteristics and information on *H. pylori* genotype, antibiotic sensitivity, and other additional data, such as giemsa staining results and histopathologic findings were recorded in a hospital registry. Available data needed for this study were gathered from that registry.

Criteria for Subject Selection

Inclusion/ Exclusion Criteria

The study by Lucentales et al. included 126 patients who were aged 18 years and older, had undergone EGD in a private tertiary institution in Quezon City, Philippines, diagnosed to have *H. pylori* infection by rapid urease test and/or histopathology, and subsequently had *H. pylori* genotype determination.[30] Subjects without available data on *H. pylori* genotype were excluded. A total of 110 subjects out of the 126 subjects were included in this study. Sixteen subjects were excluded due to incomplete data.

Description of Study Procedure

Data Gathered

The following data were extracted from the registry review: age, histopathology result, antibiotic sensitivity result, and genotypes. Likewise, additional information on treatment response following eradication therapy were collected. This information was gathered from outpatient data records and from the laboratory information system of the institution.

Description of Outcome Measures

The outcome measures of this study were the association between *H. pylori* genotypes and the following: (1) the presence of different histologic changes in the patient's gastric mucosa, (2) the antibiotic sensitivity of the organism, and (3) the treatment response of the patient. The histopathology was reported by gastrointestinal pathologists. The following histologic outcomes were noted: mild inflammation, moderate inflammation, severe inflammation, metaplasia, and carcinoma. The inflammation or gastritis was assessed using the updated Sydney Classification visual scale.[31] Antibiotic sensitivity testing was determined for the following: amoxicillin, clarithromycin, metronidazole, tetracycline, and levofloxacin. The presence of sensitivity or resistance was documented. Treatment response was labelled as either "Cure" or "Treatment Failure". Either urea breath test or *H. pylori* stool antigen test was used to determine eradication success. The different *H. pylori* genotypes were

determined by Reverse Transcription Polymerase Chain Reaction (RT-PCR).

Sample Size Estimation

The sample size was estimated using data from the study of Umbral et al., which showed *H. pylori* infection prevalence of 34% in the general population. Using a 5% margin of error, with a confidence level of 95%, the estimated minimum sample size was 371. However, the number of subjects from the registry acquired from the study of Lucentales only had a total of 126.[30] This was a limitation of the study.

Data Analysis

Frequency and percentage were used in describing the baseline characteristics of the patients, including the different genotypes, different histologic changes present, antibiotic sensitivity and the response to treatment. Fisher's Exact test was used in determining the relationship of the independent and dependent variables. SPSS (Statistical Package for the Social Sciences) was used in computing for the frequency and association tables.

Ethical Considerations

This study was done in accordance with the Principles of the Declaration of Helsinki (2013), Guidelines of the International Conference on Harmonization - Good Clinical Practice (ICH-GCP), E6 (R2) and other ICH-GCP 6 (as amended), and National Ethical Guidelines for Health and Health-Related Research (NEG HHRR), 2017. The Clinical Protocol and all relevant documents were reviewed and approved by the SLMC Institutional Ethics Review Committee. Patient confidentiality was respected by ensuring anonymity of patient records. Each patient document was coded, and did not contain any identifying information in order to ensure confidentiality. All study data were recorded, and investigators were responsible for the integrity of the data i.e. accuracy, completeness, legibility, originality, timeliness and consistency. The manner of disseminating and communicating the study results guaranteed the protection of the confidentiality of patient's data. All study-related documents such as all versions of the protocol, ethical clearance, data collection forms, hard copies of source documents, signed informed consent forms would be kept and stored by the Principal Investigator in strict confidentiality for at least 5 years; after which these would be shredded.

Results

Table 1 shows the demographic data of included subjects. A total of one hundred ten (110) subjects recorded in the *H. pylori* registry had no available data on *H. pylori* genotype; hence were excluded. Fifty-five percent (n=60) of the subjects were in the 40 to 59-year-old age group. Majority (n= 65, 59%) of the subjects were female.

Table 1. Demographics of included patients.

	Frequency	Percentage
Age (n=110)		
20 to 39	13	12
40 to 59	60	54
60 to 79	35	32
80 and above	2	2
Gender (n=110)		
Female	65	59
Male	45	41

All included subjects had available data on cagA positivity and 43% were cagA positive. Only 91 out of 110 subjects had available data on vacA and 48 (53%) were vacA positive. The vacA subunit determination showed that the s1/m2 (n=33, 69%) was the most common subunit present. Twenty-five percent (n=23/92) had both cagA and vacA genes. (Table 2). The most common histologic finding was moderate inflammation (48%) followed by intestinal metaplasia (24%). One patient had gastric adenocarcinoma on histopathology. Only 57 of the subjects had data on treatment response revealing an 87% cure rate. Urea breath test was the most common method used to check for *H. pylori* eradication. Among patients with intestinal

metaplasia, majority (n=24, 92%) had Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) stage 1 and were antrally located, which typically was considered at low risk for gastric cancer progression (Table2).

Table 2. Distribution of *Helicobacter pylori* infection based on genotype, histologic change, treatment response and antibiotic resistance.

Genotype	**Frequency**	**Percentage**
vacA (N=91)	48	53
cagA(N=110)	47	43
Both positive (N=91)	23	25
vacA subunit (N=48)		
s1/m1	15	31
s1/m2	33	69
Both negative	37	34
Histologic Findings		
Mild inflammation	20	24
Moderate inflammation	52	18
Severe inflammation	10	48
Intestinal Metaplasia	26	9
OLGIM stage 1	24	92
OLGIM stage 3	2	8
Gastric Adenocarcinoma	1	1
Response (n=53)		
Cure	46	87
Treatment failure	7	13
Antibiotic Resistance (n=54)		
Amoxicillin	0	0
Clarithromycin	12	22
Tetracycline	0	
Levofloxacin	31	57
Metronidazole	26	48

Fifty-four subjects had available data on antibiotic sensitivity to amoxicillin, clarithromycin, metronidazole, levofloxacin and tetracycline. No antibiotic resistance was noted with amoxicillin and tetracycline. The following resistance rates of 48%, 57% and, 22% were noted with metronidazole, levofloxacin and clarithromycin, respectively. (Table 2).

Positive cagA was significantly associated with intestinal metaplasia and moderate inflammation, while a negative result was associated with the presence of mild inflammation (p=0.001). (Table 3). Positive vacA was also significantly associated with moderate inflammation, while vacA negative was associated with mild inflammation (p=0.001). (Table 4). However, no association was seen when analyzed according to vacA subunits. (Table 5).

Table 3. Association of cagA positivity and histologic changes.

		Histologic Changes				
		Intestinal Metaplasia	Mild Inflammation	Moderate Inflammation	Severe Inflammation	Gastric Cancer
cagA	Positive	17(65.4%)	2 (10.0%)	26 (49.1%)	2 (20.0%)	0
	Negative	9 (34.6%)	18 (90.0%)	27 (50.9%)	8 (80.0%)	1 (100.0%)
Fisher Exact: 17.71 (P value: .001)						

Table 4. Association of vacA positivity and histologic changes.

		Histologic Changes				
		Intestinal Metaplasia	Mild Inflammation	Moderate Inflammation	Severe Inflammation	Gastric Cancer
vacA	Positive	10 (50%)	3 (16%)	29 (70.7%)	6 (60%)	0
	Negative	10 (50%)	16 (84%)	12 (29.3%)	4 (40%)	1 (100%)
Fisher Exact: 18.1 (P value: 0.001)						

When comparing the subjects with cagA plus vacA combination, cagA alone, vacA alone, and subjects who were both gene negative with histologic findings, a significant association was observed with the following combinations: gene negative and mild inflammation, vacA alone and moderate inflammation, and cagA plus vacA combination and intestinal metaplasia (p=0.008). (Table 6).

No association was seen between different genotypes, and treatment response and antibiotic sensitivity, as shown in Table 7.

Table 5. Association of vacA subunits and histologic changes.

		Histologic Changes				
		Intestinal Metaplasia	Mild Inflammation	Moderate Inflammation	Severe Inflammation	Total
vacA subunit	s1/m2	6 (60%)	1 (33.3%)	21 (72.4%)	5 (83.5%)	33 (68.7%)
	s1/m1	4 (40%)	2 (66.7%)	8 (27.6%)	1 (16.7%)	15 (31.2%)
Fisher Exact: 2.8 (p value: 0.41)						

Table 6. Association of different genotypic combinations and histologic changes.

Combinations	Histologic Changes				
	Intestinal Metaplasia	Mild Inflammation	Moderate Inflammation	Severe Inflammation	Gastric Cancer
Both Positive	7 (36.8%)	1 (5%)	13 (31.7%)	2 (20%)	0
cagA Alone	3 (15.8%)	1 (5%)	1 (2.4%)	1 (10.0%)	0
vacA Alone	3 (15.8%)	2 (10%)	17 (41.5%)	3 (30%)	0
Both Negative	6 (31.6%)	16 (80.0%)	10 (24.4%)	4 (40%)	1 (100%)
Fisher Exact: 27.4 (p value: 0.008)					

Table 7. Association of different genotypic combinations and antibiotic resistance.

Combinations	Antibiotic Resistance											
	Treatment Response n= 39		p Value	Metronidazole Resistance n= 35		p Value	Clarithromycin Resistance n= 35		p Value	Levofloxacin Resistance n= 35		p Value
	Cured	Treatment Failure		Resistant	Sensitive		Resistant	Sensitive		Resistant	Sensitive	
Both Positive	8	2	0.595	5	9	0.22	3	14	0.216	10	4	0.16
cagA Alone	3	0		2	2		1	4		4	0	
vacA Alone	10	3		8	3		5	11		7	4	
Both Negative	12	1		2	4		0	6		2	4	

Discussion

The study showed that most of the *H. pylori* infected individuals were from age 40 to 59 reflecting the recommended practice of performing gastroscopy in dyspeptic patients 45 years old and above. Further, 43% of the subjects were cagA positive. The study done by Burg et al. mentioned cagA positivity rate of 57.6%.[16,23] The cagA positivity rates in Europe ranged from 30-70%.[21] In South East Asian countries, cagA positivity could reach up to 90%.[17,18] Results of this study supported the findings of other studies done from other regions showing high cagA positivity among *H. pylori* infected individuals. This study was also able to demonstrate an association between positive cagA and, intestinal metaplasia and moderate inflammation. These findings were similar to results of several other studies which showed association of cagA positivity and a more severe gastric mucosal pathology, such as intestinal metaplasia and gastric adenocarcinoma. The study of Vadivel et al. that was done in India showed that intestinal metaplasia was associated with cagA positivity (p= 0.01).[19] It was also associated with more severe gastroduodenal lesions such as ulcerations and marked gastritis on histopathology.[20,21] Meta-analyses of case-control studies showed that CagA seropositivity was associated with 2-fold risk of distal gastric cancer among *H. pylori* infected individuals, as well as increase in the risk of peptic ulcer disease.[9] In this study, only 1 patient had gastric adenocarcinoma and was negative for cagA. Although negative cagA was less strongly linked in the development of gastric adenocarcinoma, further evidence for an association using the results of this study was lacking due to the low prevalence of the disease among subjects. This study showed association between cagA negativity and mild inflammation (p=0.001), which lend support to findings from other studies that absence of cagA gene was associated with milder pathologies. The results of this study strengthened the possibility of using cagA as a marker of more serious conditions that might require surveillance, such as the development of intestinal metaplasia and severe inflammation.

This study had vacA positivity rate of 53%, which was consistent with available studies that showed that vacA could be found in up to 70 percent of *H. pylori* infections.[27,28] The results of this study revealed that positive vacA was associated with moderate inflammation, while negative vacA was associated with mild inflammation (p=0.001). Similar

to cagA, the presence of vacA could lead to more severe diseases, such as peptic ulcer disease, MALT lymphoma, and gastric cancer, as seen in European studies.[25,34] The subunit s1/m2 (32%) was the most common subunit documented in this study. Previous studies had shown that the highest activity was in the s1m1 subunit combination. However, this was not demonstrated in this study, possibly due to the low number of subjects. When analyzed according to vacA subunits, no association was seen between the subunits and the outcomes. One cross sectional study demonstrated that vacA subunit had no association with clinical outcomes (gastritis and peptic ulcer disease).[17] The study by Hu demonstrated that the most common vacA subunits were s1m1 and s1m2, which also did not show association between subunits and gastric mucosal changes.[13] Although no association was noted with vacA subunit combination and histologic findings, it was worth mentioning that all vacA positive subjects in this study had the s1 subunit. As shown in other studies, between the two subunits (s1 and s2), the s1 was noted to be associated with significant clinical outcomes such as peptic ulcer disease and severe inflammatory activity.[6,25] The vacA s1 was significantly associated with more severe mononuclear cell infiltration (P=0.02).[18] Furthermore, a meta-analysis revealed that *H. pylori* infected individuals harboring an s1 or m1 subtype had an increased risk for developing gastric cancer in the western population (OR= 2.5-5.32).[10]

Subgroup analysis according to gene positivity: cagA+/vacA+, cagA alone, vacA alone and cag A-/vacA-, showed positive association between cagA/vacA negative and mild inflammation, vacA+ and moderate inflammation, and with cagA+/vacA+ and intestinal metaplasia (p=0.002). As earlier discussed, cagA and vacA alone could initiate an increased inflammatory response and even elevate the risk for the development of gastric cancer. This study showed that the presence of both genes, alone, or in combination, might increase the risk of developing cancer by inducing precancerous changes such as intestinal metaplasia.

This study showed that 25% of the subjects were cagA/vacA positive, and 43% were cagA positive, indicating a possible increased risk for the development of gastric cancer among included *H. pylor*i infected individuals. However, available local data showed that the incidence of gastric adenocarcinoma in the Philippines showed decreasing trend. In Metro Manila and Rizal province, a decline from an incidence rate of 11.8% to 7.5% from 1980 to 2002 was observed.[2] Upon further exploration of the cagA genotype, available studies revealed that two different cagA strains were present- the Eastern and the Western strains. These could be identified using the repeat sequences located in the 3' region of the cagA gene. Previous studies showed that the Eastern strain was more strongly linked with the development of gastric cancer than the Western strain.[35] Both in-vitro and in-vivo studies demonstrated that Eastern-type cagA protein was more carcinogenic than Western-type cagA protein.[24] The study done by Cortes et al. was the only study that explored H. pylori and its genotype here in the Philippines.[35] The study revealed that 73.7% (14/19) of the isolates were positive with cagA gene of the western type, which could possibly explain why the incidence of gastric cancer remained low despite a high incidence of *H. pylori* in the Philippines. Furthermore, as mentioned by Quebral et al., improved food preservation practices from salting and smoking to refrigeration could also partially explain the decline in gastric cancer incidence in the Philippines.[1] Other contributory factors might likely also affect the development of gastric adenocarcinoma among *H. pylori* infected patients. They mentioned that studies analyzing socio-demographic factors and the organism's genetic characteristics need to be done to better define and explore how they affect / modify carcinogenesis. Hence, combining the findings of Quebral, Cortez and the results of this study, could explain why, despite the high *H. pylori* infection rate and the high cagA and vacA positivity, a low incidence of gastric cancer was observed. This finding was similar to results of a nationwide study done in Thailand.[36] This cross-sectional study revealed that Thailand had high CagA seropositivity rate of 93%, similar to other neighboring countries such as Vietnam, Myanmar and Bhutan. However, the gastric cancer rates in those countries were higher than in Thailand. Their study further revealed that compared to Thailand that had a Western type cagA, Myanmar, Vietnam and Bhutan had Eastern type cagA.

In this study, no association was seen between different genotypes, treatment response and antibiotic sensitivity (Table 6). This was contrary

to two previous studies that showed that the presence of cagA was associated with higher eradication rates.[38,39] They mentioned that cagA and vacA s1 were associated with a more significant mucosal inflammation leading to a significant increase in blood flow to these areas. This could possibly increase the distribution of the antibiotic and could concentrate it to the affected areas. In addition, cagA and vacA s1 positive *H. pylori* were also associated with increase in the replication activity of the organism making it more susceptible to the antibiotic. Only 1 study showed no association between genotype and eradication rate.[11] This study involved patients less than 18 years old and had a small sample size (n=107). The sample size of this study could be an issue, as it decreased the power to determine the possibility of an association and then make robust conclusions. However, it was observed, from that study, as well as from this study, that most of the subjects with successful eradication had either combination of both genes or the presence of vacA, and s1 subtype; but this was not statistically significant.

There was no association seen between the different genotypes and antibiotic resistance (Table 6). This was in agreement with previous studies, which showed that vacA or cagA genes had no role in antibiotic resistance.[40,41] The presence of vacA s1 or cagA+, and especially the presence of both, was associated with more severe gastric diseases due to increased production of IL-1β and TNF-α, inducing inhibitors of secretion of hydrochloric acid and thereby increasing gastric pH; conditions that might favor the action of antibiotics.[38,39]

The limitations of this study included a low sample size, which reduced the power to make robust associations and conclusions. Furthermore, appropriate sample size might allow statistical analysis of expected outcomes that might be associated to *H. pylori* genotype including peptic ulcer disease, gastric atrophy, intestinal metaplasia and adenocarcinoma. This could better establish the association of genotypes and different outcomes according to disease severity. Being a single center study was also another limitation. *H. pylori* diversity might be a factor and was documented in other countries such as Thailand and Colombia.[36,37] If similar studies could be done from different key regions of the Philippines, this could better map the Philippine genotypic diversity and stratify risk of developing significant clinical outcomes.

Summary and Conclusion

In conclusion, cagA and vacA positivity were associated with moderate inflammatory changes in the gastric mucosa, while their absence was associated with mild inflammation. The presence of cagA gene, or combination of both genes, was associated with intestinal metaplasia. This increased the possibility of pointing to cagA as a primary genetic virulent factor of the *H. pylori* organism. However, the included patients had the western type cagA, which might pose a lower risk for the development of gastric cancer. The presence of the different *H. pylori* genotypes was not associated with treatment response and antibiotic resistance.

Author Declaration Statements

To the best of the authors' knowledge, this thesis contained no material previously published by any other person except where due acknowledgement had been made. They wished to confirm that there were no known conflicts of interest associated with this publication and there had been no significant financial support for this work that could have influenced its outcome. They also confirmed that the manuscript had been read and approved by all the named authors and that there were no other persons who satisfied the criteria for authorship that were not listed. The order of authors listed in the manuscript had been approved by all of the authors. Furthermore, an ethical clearance was secured prior to initiation of this study.

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