

Original Article

Association of *TP53* gene codon 72 polymorphism with *Helicobacter pylori*-positive non-cardia gastric cancer in Vietnam

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Abstract

Introduction: This research aimed to determine the association of the combination of *H. pylori* infection and *TP53* codon 72 polymorphism with non-cardia gastric cancer (GC) in Vietnam.

Methodology: A total of 164 patients with non-cardia GC and 164 patients with peptic ulcer disease or functional dyspepsia in controls matched by sex and age were enrolled. *H. pylori* infection was diagnosed by rapid urease test and polymerase chain reaction (PCR). The *cagA* gene-positivity and *vacA* sm subtypes were determined by multiplex PCR. Genotypes of *TP53* codon 72 polymorphism were determined by PCR-restriction fragment length polymorphism.

Results: The prevalence of *H. pylori* infection in GC and control group were 61.6% and 55.4%, respectively. The rates of *cagA*-positive strains in the two *H. pylori*-positive groups were 80.2% and 71.4%, respectively. There was no statistically significant difference in *TP53* codon 72 genotype distribution between GC group (frequencies of *Arg/Arg*, *Arg/Pro* and *Pro/Pro* genotypes were 31.1%, 43.3% and 25.6%, respectively) and controls (29.3%, 52.4% and 18.3%, respectively), $p = 0.172$. The significant difference in genotype distribution was observed in recessive model (*Pro/Pro* vs *Arg/Arg* + *Arg/Pro*) when stratifying by *H. pylori* infection (OR = 2.02, 95% CI 1.03–3.96, $p = 0.041$) and by *cagA*-positivity (OR = 2.33, 95% CI 1.07–5.07, $p = 0.032$).

Conclusions: This study suggests a synergistic interaction between *H. pylori* infection, especially *cagA*-positive *H. pylori*, and *Pro/Pro* genotype of *TP53* codon 72 polymorphism might play a significant role in the pathogenesis of GC in the Vietnamese population.

Key words: *Helicobacter pylori*; gastric cancer; *TP53* codon 72 polymorphism.

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Introduction

Gastric cancer (GC) is one of the most common cancers in the world with 1,033,701 new gastric cancer cases and 782,685 deaths were estimated worldwide in 2018 [1]. Vietnam is one of the top twenty countries having the highest prevalence of gastric cancer in 2018, with the age-standardized rates of 15.9 per 100,000 [1].

In 1994, the International Agency for Research on Cancer (IARC) classified *Helicobacter pylori* (*H. pylori*) as a group 1 carcinogen, and in 2009 the role of this infectious agent was reconfirmed in GC [2]. However, *H. pylori* strains possess a high genetic diversity with many genes encoding virulence factors that can affect clinical outcome [3,4]. The cytotoxin associated gene A (*cagA*), the vacuolating cytotoxin gene A (*vacA*) and several other virulent genes of *H. pylori* have been demonstrated as etiologic factors in gastroduodenal diseases including GC [5].

The prevalence of *H. pylori* infection in Vietnamese population was remarkably high, up to 55.5–74.6%

[6,7]. A previous investigation revealed *H. pylori* infection rate among patients with advanced non-cardia GC of 77.3% and 80.5% in Northern and Southern Vietnam, respectively [8]. To date, the accurate data regarding *H. pylori* infection in GC in central Vietnam is still lacking. A preliminary study on a small group with *H. pylori*-positive gastroduodenal diseases in central Vietnam highlighted a *cagA*-positive *H. pylori* rate of 84% [9]. The high prevalence of *H. pylori* infection and *cagA*-positivity in Vietnam supports the viewpoint that *H. pylori* virulence factors cannot be used as independent biological markers to assess GC risk in East Asian countries [10].

In addition, a number of other factors, such as host genetic variants, also play important roles in the pathogenesis of GC [10,11]. One of the most common host genes associated with many types of cancer is *TP53* (Tumor Protein 53) gene located at 17p13.1. The *TP53* gene encodes a tumor suppressor protein (p53) that induces cell cycle arrest and apoptosis in response

to DNA damage, thereby preventing tumor development [12,13]. This gene has a common single nucleotide polymorphism with guanine-to-cytosine transversion at codon 72 (CGC to CCC) in exon 4, resulting in an arginine-to-proline amino acid substitution [14]. The Arg72 isoform and the Pro72 isoform of p53 protein seem to have distinct biological functions [15,16]. Several case-control studies have been conducted to assess the association between the polymorphism at codon 72 of *TP53* and the susceptibility to GC, however the conclusions remain inconsistent [11].

Noticeably, the expression of p53 was increased in the gastric mucosa infected with *H. pylori* as demonstrated in a previous study by Jones *et al.* [17], and a significant reduction of p53 expression was observed after *H. pylori* eradication [18]. The association between the *Pro/Pro* genotype at *TP53* codon 72 and diffuse-type GC in patients with *H. pylori*-chronic gastritis was firstly reported by Hiyama *et al.* in 2002 [19]. To our best knowledge, there has no publication reporting the association of the combination of *cagA*-positivity and *TP53* codon 72 polymorphism with GC. However, patients with GC infected with *cagA*-positive *H. pylori* were significantly more likely to have *TP53* mutation than those infected with *cagA*-negative *H. pylori*, as reported by Shibata *et al.* [20]. Whether there is a synergistic effect of *H. pylori* and the *TP53* codon 72 polymorphism in GC, is not fully resolved in many countries including Vietnam. This research aimed to determine the association of the combination of *H. pylori* infection and *TP53* codon 72 polymorphism with non-cardia gastric cancer in Vietnam.

Methodology

Study population

A total of one hundred and sixty-four patients with non-cardia GC from 2012 to 2017 at Hue University Hospital (Hue, Vietnam) were enrolled in this study. GC was initially diagnosed by endoscopic lesions followed by histopathological confirmation. Four gastric biopsy specimens were taken from each GC patient, two for histopathological examination and two (one from the antrum and the other from the corpus) for *H. pylori* detection and *TP53* codon 72 polymorphism analysis. Based on histopathological examination, GC was classified into intestinal and diffuse types according to Lauren's criteria. One hundred and sixty-four patients with peptic ulcer disease (PUD) or functional dyspepsia (FD) were recruited for control group. Each control subject was matched with one GC

case by sex and age (± 2 years old). PUD was diagnosed by esophagogastroduodenoscopy, and FD was diagnosed by the Rome III classification [21] combined with esophagogastroduodenoscopy. Further, two additional biopsy specimens (one from the antrum and the other from the corpus) were taken from each control for *H. pylori* detection and *TP53* codon 72 polymorphism analysis.

Exclusion criteria included treatment with antibiotics and/or proton pump inhibitors (PPIs) and/or H_2 -receptor antagonists within 4 weeks prior to endoscopy, history of gastrectomy, and discordance between two results of determining *H. pylori* infection by rapid urease test (RUT) and polymerase chain reaction (PCR) assay.

Determining H. pylori infection

H. pylori infection in gastric biopsy specimens from the antrum and the corpus of each patient were initially detected by rapid urease test (RUT). DNA samples were then extracted from gastric biopsy specimens after RUT using Wizard genomic DNA purification kit (Promega Corp., Madison, Wisconsin, USA). The concentration and quality of extracted DNA was measured by NanoDrop 2000 UV-Vis spectrophotometer (Thermo Scientific, Wilmington, USA). Only extracted DNA samples with the A260/A280 ratio of 1.8–2.0 were included for further analysis. *H. pylori* infection was confirmed by PCR assay with primer pair targeting the *ureC* gene previously described [22]. PCR mixture contained 12.5 μ L of GoTaq Green MasterMix 2X (Promega Corp., Madison, Wisconsin, USA), 10 pmol of each primers *ureC*-F and *ureC*-R, 100 ng of template DNA in a final volume of 25 μ L. PCR reactions were performed on Applied Biosystems 2720 Thermal Cycler (Thermo Fisher Scientific, Singapore) under the temperature conditions as previously described [22]. All PCR reactions were conducted with a negative control using nuclease-free sterile water and a positive control using DNA extracted from previous *H. pylori ureC* gene-positive gastric biopsies. The 294-bp amplicons were analysed by electrophoresis on a 0.8% agarose gel. *H. pylori* infection was diagnosed if RUT and PCR results for *ureC* gene amplification were both positive.

Genotyping the cagA gene and the vacA gene of H. pylori by multiplex PCR assay

We performed multiplex PCR assay optimised by Chattopadhyay *et al.* with primer pairs targeting the *cagA* gene (*cag5c*-F and *cag3c*-R) [23], *s* (signal region) subtypes of *vacA* gene (*VAI*-F and *VAI*-R) [24] and m

(middle regions) subtypes of *vacA* gene (VAG-F and VAG-R) [25]. The multiplex PCR reaction was carried out in a final volume of 25 µL contained 12.5 µL of GoTaq Green MasterMix 2X (Promega Corp., Madison, Wisconsin, USA), 20 pmol of each primers *cag5c*-F and *cag3c*-R, 10 pmol of each primers VAI-F and VAI-R, 20 pmol of each primers VAG-F and VAG-R, 200 ng of template DNA. PCR products were subjected to 2% agarose gel electrophoresis. The amplification from regions of *cagA* gene, *vacA* s1, *vacA* s2, *vacA* m1 and *vacA* m2 yielded fragments of 350 bp, 259 bp, 286 bp, 567 bp and 642 bp, respectively. DNA extracted from previous *H. pylori* strain with *cagA*-positivity, *vacA* s1m1 and *H. pylori* strain with *cagA*-negativity, *vacA* s2m2 were included as positive control, and nuclease-free sterile water as negative control (Figure 1).

Genotyping the TP53 gene codon 72 polymorphism by PCR-restriction fragment length polymorphism (PCR-RFLP) assay

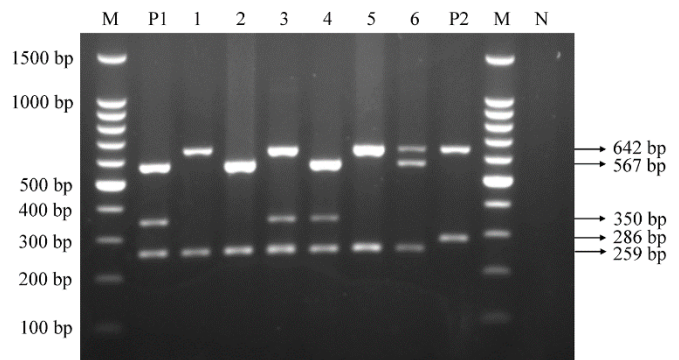
For PCR amplification, the forward primer *TP53*-F 5'-CGCAGTCAGATCCTAGCGTCGA-3' and the reverse primer *TP53*-R 5'-AGTCACAGACTTGGCTGTCCCAG-3' were designed targeting the flanking region of codon 72 of the *TP53* gene (AF: 136270, GI: 4732144, GB: AH007667) to yield a 569-bp fragment. PCR mixture contained 12.5 µL of GoTaq Green MasterMix 2X (Promega Corp., Madison, Wisconsin, USA), 10 pmol of primers *TP53*-F and *TP53*-R, 100 ng of extracted DNA in a final volume of 25 µL. The amplification reaction was performed in Applied Biosystems 2720 Thermal Cycler (Thermo Fisher Scientific, Singapore) with an initial denaturation step at 95°C for 5 minutes followed by 35 cycles at 94°C for 1 minute, 60°C for 1 minute, 72°C for 1 minute 30 seconds; and a final step at 72°C for 8 minutes. The amplicons were analyzed by electrophoresis on 0.8% agarose gel. Nuclease-free sterile water was used as a negative control. 7 µL of each amplicon was digested with 10 U of *Bsh1236I* restriction enzyme (Thermo Fisher Scientific, Vilnius, Lithuania) in a total volume of 20 µL incubated at 37°C overnight. These digested products were subjected to 2% agarose gel electrophoresis.

At codon 72, a G→C substitution (Arg to Pro) results in the loss of the original *Bsh1236I* recognition site (5'-CGCG-3'). Therefore, the amplicon of *Arg* allele is digested into two fragments (415-bp and 154-bp), whereas the one of *Pro* allele remains uncut. As a result, the *Arg/Arg* genotype yielded two digested fragments (415-bp and 154-bp), the *Pro/Pro* genotype

yielded only one product (569-bp), and the *Arg/Pro* genotype yielded three products (569-bp, 415-bp, and 154-bp) (Figure 2).

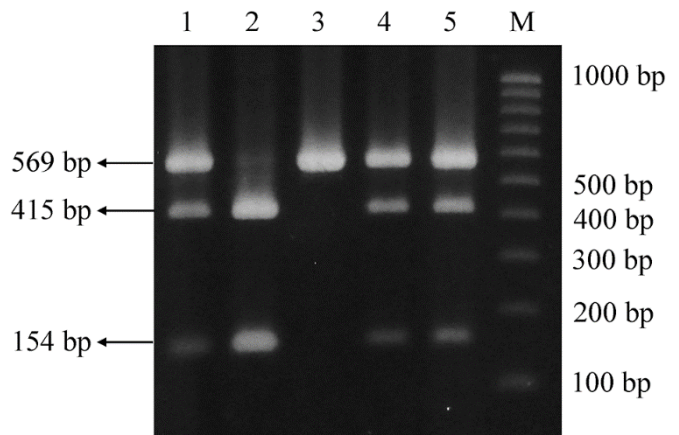
In order to optimise this PCR-RFLP assay, a number of initial samples with different genotypes (*Arg/Arg*, *Pro/Pro*, and *Arg/Pro*) were confirmed by DNA sequencing and used as positive controls.

Figure 1. Determination of the *cagA* gene and *vacA* s1, *vacA* s2, *vacA* m1, and *vacA* m2 alleles of *H. pylori* by Multiplex PCR assay.



Lane M, 100-bp marker (Promega Corp., Madison, Wisconsin, USA); lane P1, positive control 1 with *cagA*(+), *vacA* s1m1; lane 1, *cagA*(-), *vacA* s1m2; lane 2, *cagA*(-), *vacA* s1m1; lane 3, *cagA*(+), *vacA* s1m2; lane 4, *cagA*(+), *vacA* s1m1; lane 5, *cagA*(-), *vacA* s1m2; lane 6, *cagA*(-), *vacA* s1m1/m2; lane P2, positive control 2 with *cagA*(-), *vacA* s2m2; lane N, negative control (nuclease-free sterile water).

Figure 2. Determination of genotypes of *TP53* codon 72 polymorphism by PCR-RFLP assay.



Lane M, 100-bp marker (BioRad, Hercules, California, USA); lane 1, 4 and 5, *Arg/Pro* genotype; lane 2, *Arg/Arg* genotype; lane 3, *Pro/Pro* genotype.

Table 1. *H. pylori* infection, *cagA* gene and *vacA* genotypes, and the association with gastric cancer.

<i>H. pylori</i> status	Control	Gastric cancer	Univariate analysis		
	n (%)	n (%)	OR	95% CI	P-value
<i>H. pylori</i> (+) ⁽¹⁾	91 (55.4)	101 (61.6)	1.29	0.83–2.00	0.263
<i>cagA</i> (+)	65 (71.4)	81 (80.2)	1.62	0.83–3.16	0.157
<i>vacA</i> s1m1	43 (47.3)	51 (50.5)	1.14	0.65–2.01	0.654
<i>vacA</i> s1m2	46 (50.5)	45 (44.6)	0.79	0.45–1.39	0.406
<i>vacA</i> s1m1/m2 ⁽²⁾	2 (2.2)	5 (5.0)			

No *vacA* s2 subtype was found in this study; ⁽¹⁾Positivity to *H. pylori* was assessed by both rapid urease test and PCR assay of *ureC* gene; ⁽²⁾*vacA* s1m1/m2 refers to a mixture of *vacA* s1m1 and *vacA* s1m2 subtypes.

Statistical analysis

Genotype frequencies of TP53 codon 72 polymorphism were tested for Hardy-Weinberg equilibrium by Chi square test. Four different genetic models (recessive, dominant, codominant and allelic) were applied for testing the association between the TP53 codon 72 polymorphism and GC. Odds ratios (OR) and 95% confidence interval (95% CI) were calculated to evaluate the association of TP53 codon 72 polymorphism, *H. pylori* infection, and *H. pylori* genotypes, alone or in combination, with GC. The statistical analysis was performed by MedCalc statistical software v12.2.1.0 (MedCalc Software, Ostend, Belgium). The p-value ≤ 0.05 is considered statistically significant.

Results

Study characteristics

A total of one hundred and sixty-four patients with non-cardia GC were analyzed in this study, of which 66.5% were males and 33.5% females. The mean age of enrolled patients with non-cardia GC was 62.8 ± 12.4 years (range 30–93 years). Intestinal-type and diffuse-type GC accounted for 56.1% and 37.8%, respectively while 6.1% of patients with GC were typed as indeterminate according to Lauren classification.

H. pylori infection, *cagA* and *vacA* genotypes in non-cardia gastric cancer

The prevalence of *H. pylori* infection in GC and control group of PUD and FD patients in this study were

61.6% and 55.4%, respectively. The rate of *cagA*-positive *H. pylori* in GC and control group were 80.2% and 71.4%, respectively. All *H. pylori* strains in both groups carried *vacA* s1, and the *vacA* sm genotype was distributed as shown in Table 1. There was no statistically significant difference in the prevalence of *H. pylori* infection between GC and controls, as well as in the prevalence of *cagA*-positivity and *vacA* sm genotypes between *H. pylori*-positive GC and *H. pylori*-positive control groups.

TP53 codon 72 polymorphism in non-cardia gastric cancer

Hardy-Weinberg equilibrium analysis showed the compliance in GC group and control group. The frequencies of *Arg/Arg*, *Arg/Pro*, *Pro/Pro* genotypes were 31.1%, 43.3%, 25.6%, respectively in patients with GC; and 29.3%, 52.4%, 18.3%, respectively in control group. The TP53 codon 72 genotype distribution did not differ between GC group and controls ($p = 0.172$). When stratifying by Lauren's classification, no statistically significant difference in genotype distribution between GC types (intestinal-type and diffuse-type) and control group was evidenced ($p = 0.223$ and 0.370 , respectively). We neither found any statistically significant difference in genotype distribution when stratifying by *H. pylori* infection or *cagA*-positivity (Table 2).

Genetic models, including recessive, dominant, codominant and allelic models, were analyzed. None of genetic models showed association of TP53 codon 72

Table 2. TP53 codon 72 polymorphism frequencies and Hardy-Weinberg equilibrium analysis.

Group	Observed frequencies (%)			HWE	Chi-square
	<i>Arg/Arg</i>	<i>Arg/Pro</i>	<i>Pro/Pro</i>	P-value	P-value
Control	48 (29.3)	86 (52.4)	30 (18.3)	0.430	
Control with <i>H. pylori</i> (+)	25 (27.5)	49 (53.8)	17 (18.7)		
Control with <i>cagA</i> (+)	19 (29.2)	34 (52.3)	12 (18.5)		
Gastric cancer	51 (31.1)	71 (43.3)	42 (25.6)	0.092	0.172 ⁽¹⁾
GC with <i>H. pylori</i> (+)	23 (22.8)	46 (45.5)	32 (31.7)		0.119 ⁽²⁾
GC with <i>cagA</i> (+)	20 (24.7)	33 (40.7)	28 (34.6)		0.094 ⁽³⁾
Intestinal-type GC	32 (34.8)	38 (41.3)	22 (23.9)		0.223 ⁽¹⁾
Diffuse-type GC	19 (30.6)	27 (43.5)	16 (25.8)		0.370 ⁽¹⁾

HWE: Hardy-Weinberg equilibrium analysis; ⁽¹⁾ versus control; ⁽²⁾ versus control with *H. pylori* (+); ⁽³⁾ versus control with *cagA* (+).

genotypes and GC regardless of *H. pylori* status. However, when stratifying by *H. pylori* infection and *cagA*-positivity, statistically significant differences in genotype distribution were observed in recessive models (*Pro/Pro* vs *Arg/Arg* + *Arg/Pro*). Recessive model in groups with *H. pylori* infection revealed OR = 2.02, 95% CI 1.03–3.96, $p = 0.041$; and recessive model in groups with *cagA*-positivity revealed OR = 2.33, 95% CI 1.07–5.07, $p = 0.032$ (Table 3).

Discussion

H. pylori is characterized by a high level of geographically genetic diversity, and East Asian population harbors *H. pylori* strains carried GC-associated virulence factors as the *cagA* and *vacA* s1 [26–31]. These factors are thought to play an important role in the pathogenesis of gastric disease [32]. However, a number of studies in Asian cohorts have not confirmed this mechanism [33], and even “Asian paradox” was mentioned in the association between the rate of *H. pylori* infection and the risk of GC [34].

The current study highlights a high prevalence of *H. pylori* infection in both GC and controls and an extremely high prevalence of *cagA*-positivity in *H. pylori*-positive GC and *H. pylori*-positive controls. In addition, *vacA* s1 was present in all *H. pylori* strains, m1 and m2 subtypes were observed at approximately similar rates in GC and controls. Our data suggest that *H. pylori* infection, *cagA*-positivity, and *vacA* genotypes are not helpful as biomarkers to assess the development of GC in Vietnam, in accordance with other studies reporting the difficulty to explain the pathogenesis of GC by *H. pylori* infection and *cagA*-positivity due to high prevalence of these factors in Asian population [19,30]. Therefore, the attention of several researchers focused on the relationship between

bacterial and host risk factors involved in the pathogenesis of GC.

TP53 gene encodes a tumor suppressor protein (p53) that acts as a transcription regulator in order to maintain genome integrity in response to stresses [35]. The polymorphism of *TP53* at codon 72 generates two alleles, *Arg72* and *Pro72* that have different biological activities. It is known that the isoform with *Arg72* induces apoptosis better than the isoform with *Pro72*, whereas the *Pro72* isoform is more efficient than *Arg72* isoform in inducing cell-cycle arrest at G1 [36]. Moreover, other studies showed whether *TP53* mutations preferentially occurred on *Arg72* allele or *Pro72* allele depending on neoplastic tissue [37]. Notwithstanding the influence of *TP53* codon 72 polymorphism in carcinoma risk was suggested, its role remains to be clarified.

In this study, we investigated the *TP53* codon 72 polymorphism by PCR-RFLP assay. Our data is the first report of *TP53* codon 72 polymorphism in Vietnamese cohort. Hardy-Weinberg equilibrium was observed in both controls and GC group, and it demonstrated an ideal circumstance for investigation of the association between *TP53* codon 72 polymorphism and GC risk. The genotype distribution did not differ between GC and control group, this observation was similar to the findings reported by Zhang *et al.* [38] and Zhou *et al.* [39], but not in accordance with some other previous studies [40,41]. In addition, there was no significant associations between different variables (*H. pylori*-positive status, *cagA*-positivity, Lauren classification) and the different genotypes of *TP53* gene codon 72 polymorphism in GC. This result was in agreement with previous publication conducted by Khayat *et al.* [42]. To date, conclusions of the association between the *TP53* codon 72 polymorphism and the risk of GC are inconsistent partly due to

Table 3. The association of the combination of *TP53* codon 72 and *H. pylori* status with gastric cancer.

Genetic model	Regardless of <i>H. pylori</i>	<i>H. pylori</i> - positive	<i>cagA</i> -positive
	OR (95%CI)	OR (95%CI)	OR (95%CI)
Recessive			
<i>Pro/Pro</i> vs <i>Arg/Arg</i> + <i>Arg/Pro</i>	1.54 (0.91–2.61) $p = 0.111$	2.02 (1.03–3.96) $p = 0.041$	2.33 (1.07–5.07) $p = 0.032$
Dominant			
<i>Pro/Pro</i> + <i>Arg/Pro</i> vs <i>Arg/Arg</i>	0.92 (0.57–1.47) $p = 0.718$	1.28 (0.67–2.47) $p = 0.453$	1.26 (0.60–2.63) $p = 0.538$
Codominant			
<i>Pro/Pro</i> vs <i>Arg/Arg</i>	1.32 (0.71–2.43) $p = 0.377$	2.05 (0.90–4.63) $p = 0.086$	2.22 (0.88–5.58) $p = 0.091$
Allelic			
<i>Pro</i> vs <i>Arg</i>	1.12 (0.82–1.52) $p = 0.481$	1.43 (0.95–2.13) $p = 0.084$	1.51 (0.95–2.41) $p = 0.080$

geographic and ethnic discrepancies [43,44]. A review publication showed that some studies in different populations have evidenced the association between *Pro72* variant and GC, while others revealed *Arg72* variant and GC [45]. Zhang's meta-analysis indicated that *Pro* allele and *Pro/Pro* genotype were more frequent in GC than non-neoplastic Asians [11]. Therefore, in the current study, we analyzed four genetic models including recessive, dominant, codominant and allelic model, in which *Pro* allele used as a risk factor. Overall, all four genetic models showed that there was no association between the *TP53* codon 72 polymorphism and GC. Interestingly, when stratifying by *H. pylori* infection or *cagA*-positivity, recessive model (*Pro/Pro* vs *Arg/Arg* + *Arg/Pro*) revealed that *Pro/Pro* genotype was a significant risk factor in GC. Our data suggest that it is necessary to investigate a synergistic interaction between the *TP53* codon 72 polymorphism and *H. pylori* infection, especially *cagA*-positive *H. pylori*, in the pathogenesis of GC in Vietnam. Matsumoto *et al.* demonstrated that an aberrant expression of cytidine deaminase enzyme caused by *cagA*-positive *H. pylori* infection might have induced *TP53* gene mutations in gastric epithelial cells [46]. Therefore, a high prevalence of *Pro/Pro* genotype in patients with GC infected with *cagA*-positive *H. pylori* obtained in our study could be linked to this mechanism. Moreover, another mechanism to explain a higher prevalence of *TP53 Pro72* homozygous genotype in *H. pylori*-positive patients with GC than in *H. pylori*-positive controls might have related to the loss of heterozygosity (LOH). By suggesting a synergistic interaction of *cagA*-positive *H. pylori* infection and *TP53* codon 72 polymorphism that might play a significant role in the pathogenesis of non-cardia GC, we hope to contribute to identifying a more selective indication of *H. pylori* eradication as well as to assessing the possibility to use *cagA*-positive *H. pylori* infection combined with *TP53* codon 72 polymorphism as promising biomarkers of early GC. A limitation of this study was lack of *cagA* polymorphism analysis. In addition, further investigations with larger samples of participants are necessary to clarify this issue.

Conclusion

Our findings showed that of *H. pylori* infection, *cagA*-positivity, *vacA* genotypes, and *TP53* codon 72 polymorphism are not independent risk factors of gastric cancer. A synergistic interaction between *H. pylori* infection, especially *cagA*-positive *H. pylori*, and *Pro/Pro* genotype of *TP53* codon 72 polymorphism

might play a significant role in the pathogenesis of gastric cancer in the Vietnamese population.

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Ethical approval

This study was approved by the Ethics Committee of Hue University of Medicine and Pharmacy, Hue University (Hue, Vietnam). All participants in the study received prior informed consent.

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