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Is There A Role of Helicobacter Pylori Infection in Incidence of Acute Coronary Syndrome?

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Background: There is a growing interest in the bacterium's association in extragastric diseases such as cardiovascular, neurological, hematological and uro-gynecological diseases.

Aim: We aimed to investigate the correlation between acute coronary syndrome (ACS) and chronic infection of *Helicobacter pylori* (*H.pylori)* in Egyptian population.

Methods: We prospectively evaluated 119 patients (from December 2016- February 2017) presented with typical chest pain and/or percutaneous coronary intervention revealed ACS are investigated to *H.Pylori* infection by antibodies (Ab) test of both acute and chronic infection. IgM and IgG tests respectively to evaluate the association between ACS and *H.pylori* infection. Univariable and multivariable Cox proportion hazards regression with a 95% confidence interval (CI) was used to measure the crude hazard ratio (HR) and adjusted HR (aHR) of ACS for the *H.pylori* infection.

Results: The mean age of the study population was 57.9 ±11.2 [standard deviation (SD)] and having comorbidities like diabetes (46.2%), and hypertension (42%). ACS was confirmed in 94% of the whole study sample with *H.pylori* IgG antibodies (mean±SD: 2.36± 1.42 U/mL). The risk of developing ACS was significantly associated and increased with increasing age. The risk of developing ACS in patients with higher *H.pylori* IgG was 1.6 times (95% CI: 0.662-1.704). We also estimated the risk of ACS in relation to family history, the risk of developing ACS was nearly two-fold higher in patients with existence of family history of CVDs.

Conclusion: However there are many presented with ACS, current risk factors cannot explain their ACS, hence chronic H. Pylori infection may play a role, need further researches evaluate the real condition.

Keywords: Acute coronary syndrome, Helicobacter pylori, Cardiovascular disease, Bacterial infection, extragastric manifestation, Egypt.

1 Introduction

Coronary artery diseases (CADs) are leading cause of mortality and morbidity in the modern world, a major public health problem. Acute coronary syndrome is a crucial stage of the clinical manifestation of CAD and results in substantial morbidity and mortality [1]. However, research in ACS has propelled the field from one driven by anecdote to one guided by scientific evidence. For instance, pioneer findings identified the relationship of chronic infections influence on ACS and CADs [2,3]. The role of virus and bacterial pathogens including *helicobacter pylori* (*H.pylori*) are now considered as factors implicated in development of ACS [3-7]. *H.pylori* is the most common chronic bacterial infection of the human upper gastrointestinal tract. Recent evidence from Taiwan's national retrospective cohort study identified a greater relationship between *H.pylori* and ACS [4]. However, a higher percentage of 91.7% seropositive *H.pylori* antibodies identified among Egyptian population [8]. Similarly, a national representative survey in Egypt found an adjusted overall prevalence of CAD of 8.3% [9]. Further investigating this among Egyptian sample may provide an interesting insight to clarify the relationship between *H.pylori* and ACS. Therefore, we aimed to investigate the correlation between ACS and chronic infection of *H.pylori* in Egyptian population.

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2 Methods

The study population consisted of 119 patients presented with typical chest pain and/or percutaneous coronary intervention revealed ACS are investigated to *H.pylori* infection by Ab test of both acute and chronic infection. IgM and IgG tests respectively to evaluate the association between ACS and *H.pylori* infection. Patients with acute inflammatory diseases, renal failure, autoimmune diseases and current use of steroid within the last 3 months were excluded. Informed consent was obtained from each participant prior to their study participation.

2.1 Determination of risk factors

Hypertension was diagnosed in patients who are using antihypertensive medications or diagnosed as hypertensive (blood pressure >140/90 mmHg). Diabetes mellitus was confirmed if the fasting blood sugar level >123 mg/dl or receiving insulin or oral antidiabetic medications.

2.2 Laboratory methods

A small amount of blood sample (9 vol.) was collected by an experienced technician into Diatube H (Becton Dickison) and titrated with 0.109 M trisodium citrate anticoagulant (1 vol.) at hospital admission. Samples were centrifuged for 10 min at 3,000 9g at a temperature of about 4C and serums were stored -30C until analysis. The samples were assayed by using enzyme linked immunosorbent assay (ELISA) and quantitative polymerase chain reaction (qPCR) tests for IgG antibodies directed against HP (Euroimmun, Germany) in microbiology and immunology departments in Aswan university hospital and 6th October university hospital, Egypt. As per the manufacturer's instructions, seropositivity was defined as an IgG titer of at least 22 RU/ml.

2.3 Statistical analysis

The descriptive data were summarized as frequencies, percentages, and mean with standard deviations (SD). Univariable and multivariable Cox proportion hazards regression with a 95% confidence interval (CI) was used to measure the crude hazard ratio (HR) and adjusted HR (aHR) of ACS for the *H.pylori* infection, after controlling for sex, age, sex, comorbidities, presence of cardiac troponin, family history and *H.pylori* IgG. All the statistical analysis was performed using SPSS 22.0 (SPSS Inc., Cary, NC, USA). P<0.05 in 2-tailed tests was considered significant.

3 Results

We prospectively screened 119 patients with ACS from December 2016 to February 2017 attending Aswan university hospital and 6Th October university hospital. The mean age of the study population was 57.9 ±11.2 [standard deviation (SD)] and having comorbidities like diabetes (46.2%), and hypertension (42%). However, 20.2% of these patients had a family history of CVDs. Fifty nine patients has chest pain duration was less than six hours and more than half of the patients had hospital stay of 3 days [Table 1].

Table 1: Baseline characteristics (N=119)

	Total	**Percentage**
Sex		
Male	82	68.9
Female	37	31.1
Age (Mean±SD)	57.9 ±11.2	-
Diabetes mellitus	55	46.2
Hypertension	50	42.0
Family history of CVDs	24	20.2
Duration of chest pain		
1-6 hours	59	49.5
7-12 hours	22	18.5
>12 hours	38	32.0
Hospital stay		
1 day	1	0.8
2 days	43	36.1
3 days	61	51.2
4 days	10	8.4
5 days	3	2.5
7 days	1	0.8

SD: standard deviation; CVDs: cardiovascular diseases

Table 2: Clinical features of study population (N=119)

	N (%)
Acute coronary syndrome (yes)	112 (94.1%)
H.pylori IgG antibodies (positive)	
1.1-2.0 U/mL	46 (38.6%)
2.1-3.0 U/mL	29 (24.3%)
3.1-4.0 U/mL	23 (19.3%)
>4.0 U/mL	21 (17.6%)
ECG changes	
Normal	10 (8.4%)
ACS	11 (9.2%)
Depressed ST	24 (20.1%)
Anterior STEMI	10 (8.4%)
Inferior STEMI	4 (3.3%)
Dynamic ST	7 (5.8%)
Elevated ST	9 (7.5%)
Inverted T wave	14 (11.7%)
Q wave changes	11 (9.2%)
Others*	19 (16%)
Troponin (positive)	50 (42%)

Others: left bundle branch block-6, late STEMI-2, neglected anterior-1, no ST wave-3, wandering-1, supraventricular tachycardia- 1, ventricular tachycardia-1, biphasic T wave-1, Nonsustained ventricular tachycardia-1, sinus rythms-1, atrial flutter-1

Table 2 summarises the clinical and laboratory evaluation of risk factors among the participants at the time of enrollment. ACS was confirmed in 94% of the whole study sample with *H.pylori* IgG antibodies (mean±SD: 2.36± 1.42 U/mL). Greater summed ST segments, inverted T wave and Q wave changes were the most common ECG changes observed. Cardiac troponin (cTn) was positive in fifty patients that determined ACS.

The risk of developing ACS was significantly associated and

Table 3: Cox model measured hazards ratios and 95% confidence intervals of ACS associated with Helicobacter pylori infection and covariates.

	Crude Hazards ratio (95% CI)	Adjusted Hazards ratio[a] (95% CI)
Age (years)		
≤49	1 (Reference)	1 (Reference)
50-64	0.999 (0.361-1.165)	0.873 (0.247-1.015)*
65-74	2.082 (0.998-1.184)*	1.890 (0.689-2.648)**
75+	3.168 (0.762-1.889)**	3.104 (2.741-3.968)**
Sex (female vs male)	1.136 (0.210-6.145)	1.327 (1.124-1.831)**
Baseline co-morbidities (yes vs no)		
Hypertension	0.805 (0.152-4.251)*	0.674 (0.129-0.897)
Diabetes	1.515 (0.289-7.934)**	1.482 (0.118-1.729)**
Troponin (positive vs negative)	4.936 (0.527-46.187)**	2.476 (1.962-2.814)**
H.pylori IgG	1.720 (0.826-3.582)**	1.596 (0.662-1.704)**
Family history of CVDs	3.250 (0.676-15.627)*	1.931 (1.633-2.214)**

[a] Multivariable analysis including adjustment for age, sex, and comorbidities of hypertension, diabetes, and family history of CVDs. *p<0.05, **p<0.01

increased with increasing age. The aHR of ACS was 1.32 times higher in men than women (95% CI: 1.12-1.83). Comorbidities such as diabetes (aHR= 1.482; 95% CI: 0.11-1.73) and higher cTn levels (aHR= 2.47; 95% CI: 1.962-2.814) poses higher risk of ACS patients. The risk of developing ACS in patients with higher *H.pylori* IgG was 1.6 times (95% CI: 0.662-1.704). We also estimated the risk of ACS in relation to family history, the risk of developing ACS was nearly two-fold higher in patients with existence of family history of CVDs [Table 3].

4 Discussion

In this study, we prospectively evaluated the effects of *H.pylori* seropositivity among 119 patients presenting with ACS in Egypt. The main findings of this study showed a positive association between *H.pylori* seropositivity and ACS in Egyptian population. The risk of developing ACS in patients with chronic *H.pylori* increased with the presence of age, sex, diabetes, and family history of CVDs. The risk of developing ACS in patients with *H.pylori* increased with the presence of any comorbidities and seropositivity of *H.pylori* IgG and cardiac troponin.

Previous studies have shown a positive association between *H.pylori* with cardiovascular risk factors, particularly ACS. A recent meta-analysis involving studies published from 1992 to 2014 identified an increased risk of 11% (RR 1.11; 95% CI: 1.01-1.22) of CHD in *H.pylori* infected patients [11]. Studies conducted in Taiwan [4], Iran [7,12], Singapore [13] and South Korea [14] have also shown that *H.pylori* is associated increased risk of ACS. In the present study, we confirmed the presence of a significant association between chronic *H.pylori* infection with higher IgG (>1.1 U/mL) and electrocardiographically confirmed ACS.

Several countries like Egypt (91.7%), Republic of Korea (80.8%), Latvia (79.2%), Japan (75%), Chile (73%), China (71.4%) and Mexico (66%) are at high prevalence of *H.pylori* infections [8,15-20]. Thus, delayed eradiation of *H.pylori* infection may reduce the emerging burden of cardiovascular diseases including ACS and investigating more aggressive treatment for chronic *H.pylori* patients may be necessary. However, proton-pump inhibitors (PPIs) - based triple therapy (2-PPIs, amoxicillin, and clarithromycin) are currently used as eradication regimens for *H.pylori* [21]. Mounting evidence demonstrated that PPI's are associated with a number of adverse effects including reduced antiplatelet effect of clopidogrel. This findings led the FDA in 2009 to warn against clopidogrel and PPI's combination [22]. A recent meta-analysis of 31 observational studies found that concomitant use of PPIs with clopidogrel have about a 30% increased risk of cardiovascular events compared with nonusers of PPIs [23]. Therefore, more caution is required while using PPIs while more cardiovascular safety of concern.

Traditional risk factors including hypertension, diabetes mellitus, smoking, obesity, dyslipidemia and positive family history of CVDs may lead to ACS. However, considering our findings, chronic *H.pylori* was found to be one of the risk factor for CAD. Similar findings seen in *Kowalski et al.* study [24] where CAD subjects were significantly more frequently seropositive to *H.pylori* than control group (81.5% vs. 51%, p<0.05). Interestingly, Budzynski's open-label study found that risk of hospitalization due to ACS was higher in patients undertaking *H.pylori* eradicative therapy during a 2.5 years of follow-up [25].

In this study, *H.pylori* serological determination was used to confirm the H.pylori infection in ACS patients. To resume, anti-*Hp* IgG and anti-CagA antibodies are the most commonly used to detect active *H.pylori* infection. Similar to our findings, *Jafarzadeh et al.* on Iranian patients identified a greater seroprevalence of anti-Hp IgG antibodies in patients with acute myocardial infraction (86.7%) and unstable angina (91.7%) [26]. Future investigation can focus on serological evaluation among current and past *H.pylori* infected patients in the ACS in relation to *H.pylori* strain diversity should be considered.

5 Conclusion

However there are many presented with ACS, current risk factors cannot explain their ACS, hence chronic *H. Pylori* infection may play a role, need further researches evaluate

the real condition.

Conflict of Interest

All authors declared no conflict of interest with this research work.

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