# Prognostic value of the Serological Response to *Helicobacter Pylori* in the Long-Term Outcomes of Acute Coronary Syndrome

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## SUMMARY

### Background
The serological response to *Helicobacter pylori* (HP) has been recognized as a cardiovascular risk factor. Yet, its prognostic usefulness in acute coronary syndromes (ACS) has not been extensively evaluated.

### Objective
To identify the prevalence and long-term prognosis of abnormalities in the level of IgG antibodies against HP (HP-IgG) in patients with ACS.

### Material and Methods
From April 2003 to December 2003, a total of 67 consecutive patients hospitalized due to ACS (unstable angina [UA], acute myocardial infarction [AMI]) within 24 hours from symptoms onset were evaluated using a commercial immunoassay kit (Meridian Diagnostics, USA).

### Results
During follow-up (12±3 months) 10 (14.6%) events were reported (death/AMI/rehospitalization due to UA). The area under the ROC curve using HP-IgG to predict events was 0.85±0.06 (95% CI, 0.74-0.96); the cut-off point of 185 IU had a sensitivity of 70% and a specificity of 82%. Patients were divided into 2 groups: group 1 (HP-IgG >185 IU, 25.4%) and group 2 (HP-IgG <185 IU). Both groups were comparable. Annual survival free from events was 67% versus 90% in groups 1 and 2, respectively (log-rank test, p=0.01). The variables identified at admission as independent predictors of events were HP-IgG >185 UI (hazard ratio [HR]=5.588; p=0.039), hypotension (HR=1.109; p=0.035) and elevated creatinine levels (HR=1.997; p=0.019).

### Conclusions
Early elevation of HP-IgG levels was present in 25% of patients with ACS and levels > 185 IU were associated with poor long-term outcomes.

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**Key words** > Acute Coronary Syndrome- *Helicobacter pylori* - Prognosis

**Abbreviations** >

| | | | |
|---|---|---|---|
| **UA** | Unstable angina | **HP-IgG** | Immunoglobulin G antibodies against *Helicobacter Pylori* |
| **CK-MB** | Creatine kinase MB fraction | **AMI** | Acute myocardial infarction |
| **ECG** | Electrocardiogram | **ACS** | Acute coronary syndrome |
| **HP** | *Helicobacter pylori* | **ICCU** | Intensive Coronary Care Unit |

## BACKGROUND

Numerous risk factors for atherosclerosis have been identified, yet, as not all patients present them, the search for new risk factors that may contribute to the progression of the disease is promising. (1) Different pathogen infections have been attributed to the development of coronary artery disease. (2-4)

Cytomegalovirus, herpes virus, *Chlamydia pneumoniae* and *Helicobacter pylori* (HP) have been associated with atherosclerosis. (4-6) The concept that chronic infections increase the risk in these patients has also been reported. (7-11)

Little is known about the importance of antibody

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titers of immunoglobulin against HP in acute coronary syndromes with and without ST-segment elevation. The hypothesis of the present paper was that patients with ACS and high levels of this marker have poor long-term outcomes.

The goal of this study was to identify the prevalence and long-term prognosis of abnormalities in the level of IgG antibodies against *Helicobacter pylori* (HP-IgG) in patients with ACS.

## MATERIAL AND METHODS

### Population

We conducted an observational and prospective study including 67 consecutive patients admitted to the Coronary Care Unit of the *Instituto de Cardiología de Corrientes* with ACS (UA, AMI) within 24 hours from symptoms onset between April and December 2003. All patients fulfilled inclusion criteria.

#### *Inclusion criteria*

*Acute coronary syndrome*, defined as typical chest pain ≥ 20 minutes with at least one of the following: new or presumably new ST-segment elevation or depression, rise in cardiac biomarkers (CK-MB above the upper reference limit in ≥ 2 samples obtained in an interval > 6 h and or Troponin T ≥ 0.02 ng/ml.

*Acute myocardial infarction*, confirmed by two out of three of the following criteria: 1) typical chest pain lasting 30 minutes or greater, 2) raise in CK-MB twice the upper reference limit or troponine T > 0.1 ng/dl, and 3) development of new Q waves. Minimal myocardial damage was defined as troponin T between 0.02 and 0.1ng/dl.

#### *Exclusion criteria*

The following were considered exclusion criteria: admission after 24 h from symptoms onset, febrile syndrome, any inflammatory or infectious disease in the previous month, secondary angina, active digestive tract bleeding (within the last 15 days), acid-sensitive syndrome under treatment within the last 3 months, use of antibiotics (30 days), history of collagen diseases or rheumatic disorders, cardiogenic shock, acute pulmonary edema, suspected myocarditis, pulmonary thromboembolism, congenital diseases, dilated cardiomyopathy, hypertrophic cardiomyopathy, heart valve disease, pericardial disease or difficulty to complete follow-up.

### Study protocol

The study protocol was approved by the Teaching and Research Committee of our institution. All patients were informed about their inclusion in the study and signed an informed consent form. All the participants underwent complete medical history, physical examination, 12-lead ECG at admission and 2 h after reperfusion strategy in patients with ST-segment elevation, and chest X-ray at admission and at 24 h. After admission, HP-IgG levels were determined using a commercial enzyme immunoassay kit (Meridian Diagnostics, USA). Blood glucose levels, creatinine levels, troponin T and cardiac enzymes (CK, CK-MB) were also measured. Biomarkers were determined 2 h after admission or reperfusion strategy, and at 6, 12 and 24 h and thereafter once daily until the values returned to the normal range. The cut-off value of HP-IgG was determined by using a ROC curve.

### Follow-up and definitions

Mortality, infarction and rehospitalization due to UA were evaluated from admission to the first year. Mortality of all cause was considered. Acute myocardial infarction was defined by two out of three of the following criteria: 1) typical chest pain lasting 30 minutes or greater, 2) raise in CK-MB twice the upper reference limit or troponin T > 0.1 ng/dl, and, 3) development of new Q waves. Rehospitalization due to UA was defined as any admission due to typical chest pain lasting > 10 minutes with ECG changes, with or without rise in troponin (0.02 and 0.099 ng/dl). We used the records of our institution for patients' follow-up, and the information was obtained during medical visits or by telephone call. Mean follow-up was 12 ± 3 month.

### Management of hospitalized patients

All patients received 100 - 200 mg of aspirin after admission and once a day thereafter. Patients with ST-segment elevation within 12 hours from symptoms onset underwent primary angioplasty or thrombolytic therapy.

### Statistical Analysis

A ROC (receiver operator characteristic) curve was built to determine the best cut-off value of HP-IgG for predicting events. The characteristics of patients with HP-IgG levels higher, lower or equal to the cut-off value were compared using chi-square test for qualitative variables, and the results were expressed as percentages. Quantitative variables were expressed as median with the corresponding interquartile interval and were analyzed using Student's t test or Mann-Whitney U test for variables of normal or abnormal distribution, respectively. Cox proportional hazards model was used to identify independent predictors of events using the following variables: age, male gender, HP-IgG, systolic blood pressure, creatinine levels, diagnosis of infarction, diabetes, smoking habits, site of infarction and ventricular function. The beta coefficient for systolic blood pressure was negative. P value < 5 and alpha error < 0.8 were considered statistically significant. Survival curves were built with the Kaplan-Meier method and were compared using log-rank test. Statistical analysis was performed using SPSS 10.0 statistical package for Windows (SPSS Inc., Chicago, Illinois, USA).

## RESULTS

### Characteristics of the population

The demographic characteristics of the population are detailed in Table 1. Mean HP-IgG was 144 ± 115 IU. The incidence of events (mortality/AMI/rehospitalization due to UA) was 14.92% (10/67). A ROC curve was built to determine the best cut-off value of HP-IgG for predicting events. The area under the ROC curve was 0.85 ± 0.06 (95% CI 0.74-0.96) (Figure 1). A cut-off value of 185 IU showed a sensitivity of 70% and specificity of 82%. A total of 17 patients (25.4%) had HP-IgG values > 185 IU at admission (group 1); the remaining patients constituted group 2. The basal characteristics were similar in both groups. AMI was diagnosed in 59% versus 50% of patients in groups 1 and 2, respectively (Table 1).

Complementary tests after hospitalization were similar between both groups (Table 2).

**Table 1.** Demographic characteristics of patients with HP-IgG > and ≤ 185 IU

| Variable | HP-IgG > 185 IU (Group 1) | HP-IgG ≤ 185 IU (Group 2) | p |
|---|---|---|---|
| Age, median (interquartile range) | 63 (53-72) | 60 (51-68) | 0.47 |
| Male gender | 82% | 75.8% | 0.25 |
| Hypertension | 55% | 53% | 0.44 |
| Dyslipemia | 40% | 41% | 0.43 |
| Diabetes | 35.3% | 25.2% | 0.20 |
| Acute myocardial infarction | 85% | 84% | 0.64 |
| Minimal myocardial damage | 15% | 16% | 0.58 |
| Thrombolytic agents | 18% | 17.2% | 0,.55 |
| Primary angioplasty | 22% | 21% | 0.47 |
| Coronary anogiography | 77% | 75.8% | 0.32 |
| Killip | | | |
| I | 57% | 58% | 0.51 |
| II | 43% | 42% | |

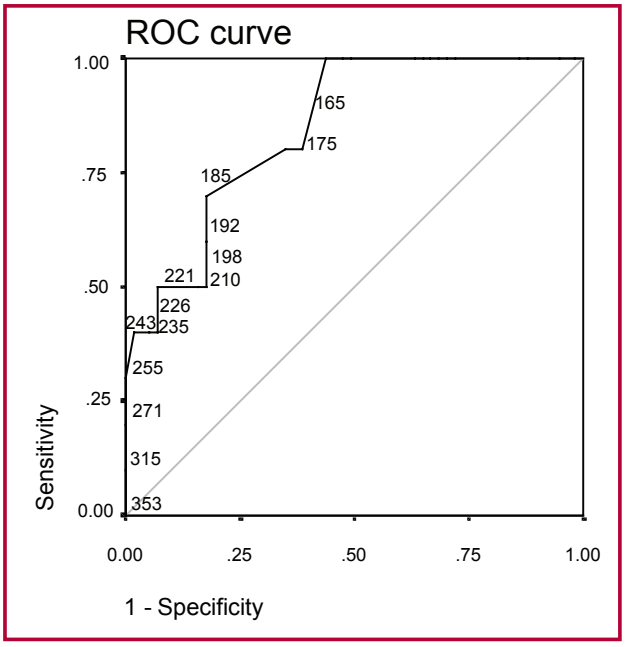


**Fig. 1.** ROC curve using HP-IgG to predict mortality/infarction/rehospitalization due to unstable angina during follow-up. Area under the curve: 0.85 ± 0.06 (95% CI 0.74-0.96), cut-off value: 185 mg/dl, sensitivity: 70%, specificity: 82%.

### Predictors of mortality and survival analysis

Seven patients (41%) in group 1 vs. 3 patients (6%) in group 2 presented events (mortality/AMI/rehospitalization due to UA). Mortality was 23% (4 patients) vs. 0% (0 patients) in groups 1 and 2 (p = 0.003), respectively. Infarction/reinfarction occurred in 11.8% (2 patients) vs. 2% (1 patient), and hospitalization due to angina in 11.8% (2 patients) vs. 4% (2 patients) in groups 1 and 2, respectively (Figure 2).

HP-IgG values were significantly different between patients with and without events.

The variables identified at admission as independent predictors of events were HP-IgG > 185 IU (hazard ratio [HR] = 5.588; p = 0.039; 95% CI 1.091-28.62), hypotension (HR = 1.109; p = 0.035; 95% CI 1.007-1.21) and elevated creatinine levels (HR = 1.997; 95% CI 1.244-16.369; p = 0.019) (Table 3).

Annual survival rate free of events was 67% versus 90% in groups 1 and 2, respectively (log rank test p < 0.001) (Figure 3). Mean follow-up was 12 ± 3 months and was completed by all patients.

## DISCUSSION

This study, conducted on an unselected population of patients with ACS admitted within 24 hours from symptoms onset, showed that HP-IgG values > 185 IU present in 1 out of 4 patients, were associated with increased risk pf events in the long-term.

### Infection, inflammation and acute coronary syndrome

Several epidemiological studies demonstrated an association between atherosclerosis and antibodies against pathogens. (1) Vascular inflammation is considered a key component in the genesis of atherosclerosis. (13) Infections may contribute to the development of atherosclerosis and may as well trigger plaque rupture, leading to an acute thrombotic event. Clinical observations support the concept that systemic inflammation is influenced by plaque instability. There is evidence about systemic inflammation in patients with AMI, reflected by high levels of C-reactive protein and amyloid protein. (3, 7, 14) Persistent inflammatory response is present in cytomegalovirus, Helicobacter pylori or Mycoplasma seropositivity. (2) Increased levels of markers for macrophage activity have been associated with the presence of multiple complex plaques in patients

| Variable (median, IQR) | HP-IgG > 185 IU (Group 1) | HP-IgG ≤ 185 IU (Group 2) | p |
|---|---|---|---|
| Hematocrit, % | 39 (36-41.2) | 40 (37-42 | 0.34 |
| Creatinine levels, mg/dl | 1.21 (0.99-1.24) | 1.08 (0.92-1.24) | 0.22 |
| cTnT at admission, ng/dl | 0.32 (0.02-0.54) | 0.1 (0.02-0.18) | 0.44 |
| White blood cell count, mm3 | 9800 (7300-11500) | 11000 (7500-13000) | 0.28 |
| Maximal CK, IU | 370 (165-1870) | 964 (99-1724) | 0.78 |

cTnT: Cardiac troponin T. CK: Creatine kinase

**Table 2.** Complementary tests in groups 1 and 2

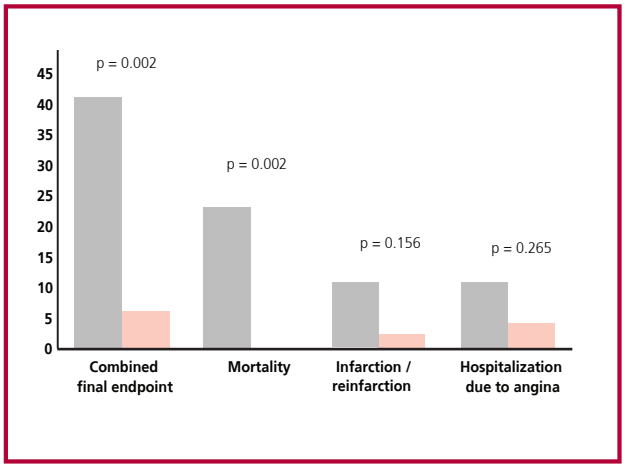


**Fig. 2.** Events during follow-up.

with UA, (3, 15) and documented in necropsy studies, confirming the systemic nature of this disease. (15) Recently, the hypothesis of the inflammatory theory has gained interest. Greater exposure to infections, rather than a specific infection, increases the risk of acute coronary events in vulnerable patients. (5, 14, 16, 17)

## Relation between Helicobacter pylori and events

There is contradictory information about the association between HP infection and coronary artery disease (11, 18-20) due to the size and design of the studies, and the lack of control for confounding factors, such as socio-economic classes. (21) Previous studies have reported adverse outcomes in patients with positive HP serology. (22) Elizalde et al. identified risk factors present at the moment of hospitalization (RR 2.58) and final HP status (RR 3.07) as independent predictors of recurrence of acute coronary events during follow-up. (23) Gunn et al. reported that, in subjects < 65 years old, cytotoxin associated gene-A antigen seropositivity was related with a 1.8-fold increase in myocardial infarction risk, which increased further to 2.25-fold in subjects < 55 years. (24)

In the present paper, HP-IgG > 185 IU was associated with a risk of events of 5.188, and persisted after adjusting for other covariables (RR 5.58), together with hypotension at admission and elevated creatinine levels. Elizalde et al. observed that recurrences of events were greater at 6 and 12 months in patients HP-positive, 35% and 55%, respectively, compared to patients in whom the bacteria was eradicated (10% and 25%, respectively). (23) In our study, the incidence of events was greater in patients with HP-IgG > 185 IU compared to patients with HP-IgG level below this cut-off value: 41% versus 6%. Mortality was 23% (4 patients) versus 0% in groups 1 and 2, respectively. Infarction/reinfarction occurred in 11.8% versus 2% and hospitalization due to angina in 11.8% versus 4% in groups 1 and 2, respectively. HP-IgG values were significantly different between patients with and without events; yet CRP levels were similar at admission and after 24 hours.

In the case-control study by Koenig et al., the association of positive IgA or IgG for HP with stable coronary artery disease was moderate and was no longer statistically significant after controlling for potential confounders. (25) An alternative explanation has been put forward, suggesting that variations in the strength of HP strains to provoke an inflammatory response might play a crucial role in the relation with coronary artery disease. (26, 27) CagA positive strains are associated with peptic ulcer and severe gastritis. (28, 29) Increased expression of interleukin-1 and interleukin-8 in the gastric mucosa is observed in the most severe types of gastrointestinal disease. (26) Markers of systemic inflammatory response have not been reported in this setting. (25) In addition, positive HP serology was significantly higher in patients with multivessel disease (3, 46) compared to patients with single-vessel disease (2.86, p = 0.030 and 2.78, p = 0.008, respectively). The association between coronary artery disease and HP infection was more significant among Japanese patients without any history of diabetes or smoking. (30) This information means that the association between HP infection and coronary artery disease is clinically relevant. (25)

Hypotension at admission was also a prognostic marker: for each 1 mm Hg reduction in blood pressure the risk increased by 10%, as it has been reported by previous studies. (31)

In agreement with recent publications, creatinine level was a strong predictor of risk. (32, 33) Most previous studies reporting the prevalence of kidney dysfunction in patients with ACS were based on selected populations (patients hospitalized coronary

**Table 1.** Predictors of events using Cox proportional hazards model

**HP-IgG > 185 IU: HR = 5.188 (95% CI 1.301-20.698)**
**Adjusted Cox regression**

| Variable | p | Hazard ratio | Lower limit | Upper limit |
|---|---|---|---|---|
| HP-IgG > 185 IU (Yes/No) | 0.039 | 5.588 | 1.091 | 28.62 |
| Age (years) | 0.148 | 0.932 | 0.847 | 1.025 |
| Male gender (Yes/No) | 0.119 | 0.145 | 0.013 | 1,.9441 |
| Systolic BP at admission (mm Hg) | 0.035 | 1.109 | 1.007 | 1.221 |
| Creatinine levels (mg/dl) | 0.019 | 1.997 | 1.244 | 16.369 |
| Smoking habits (Yes/No) | 0.668 | 0.865 | 0.802 | 1.859 |
| Diabetes (Yes/No) | 0.056 | 1.008 | 0.958 | 1.748 |
| Site of infarction (Yes/No) | 0.473 | 1.105 | 0.984 | 1.627 |
| Ventricular function, % | 0.067 | 1.064 | 0.941 | 1.591 |
| Diagnosis of infarction (Yes/No) | 0.051 | 3.600 | 2.001 | 6.600 |

HP-IgG: Immunoglobulin G Antibodies against *Helicobacter Pylori*. SBP: Systolic blood pressure.

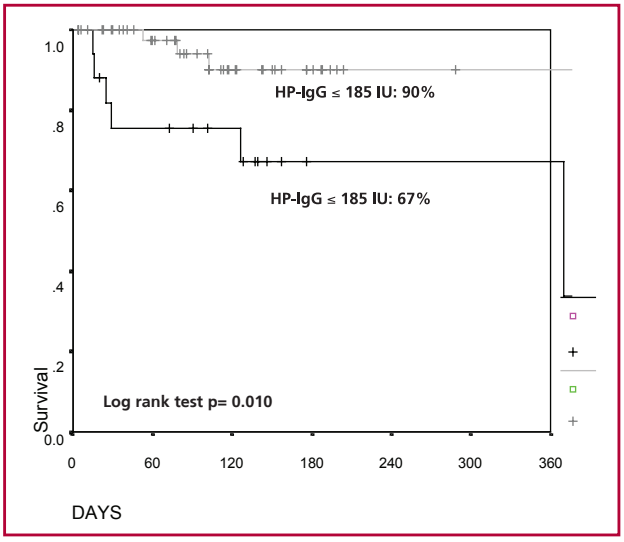


**Fig. 3.** Survival free of events curve.

care unit or included in clinical trials) that excluded these patients to a greater or lesser extent.

## Survival

In younger individuals in Japan, HP infection is significantly associated with coronary artery disease and risk of ischemic events. (34) We found an event-free survival of 90% in patients with HP-IgG ≤ 185 IU and of 67% in those with HP serology > 185 IU. Taking a thorough look, both curves start separating during hospital discharge, and the difference is more pronounced after 30 days, showing that higher levels of this marker at admission allows selecting a group of patients at higher clinical risk.

## Study limitations

The small number of patients is the main limitation of the study. As we only measured IgG antibodies against HP, the result may reflect past exposure to HP instead of active infection. The determination of this marker using urea breath test and histological examination of gastric mucosal biopsy specimens are useful to detect active infection by HP; however, they were not used in our study.

## Clinical implications

This study suggests the presence of inflammation in the setting of ACS, expressed by the presence of IgG antibodies against Helicobacter pylori. A cut-off value of 185 IU identified a group of patients at high risk of events during follow-up and with lower survival at one year. (35, 36) Further registries should be designed to confirm these findings in order to evaluate the presence of this infection and to bring relevance to the infections associated in patients hospitalized due to this syndrome. The results might be useful to start eradication treatments and prevent subsequent infections which might be responsible for recurrent episodes. (23, 36, 37)

# CONCLUSIONS

One out of four patients with acute coronary syndrome had high levels of HP-IgG within 24 hours from admission. Levels of HP-IgG > 185 IU were associated with poor long-term outcomes. This association might be confirmed by further studies with eradication treatments.

# RESUMEN


## Valor pronóstico de la respuesta serológica debida a *Helicobacter pylori* en la evolución a largo plazo del síndrome coronario agudo

### Introducción

La respuesta serológica a *Helicobacter pylori* (HP) se ha reconocido como un factor de riesgo cardiovascular. Sin

embargo, su utilidad pronóstica en síndromes coronarios agudos (SCA) fue escasamente evaluada.

**Objetivo**

Identificar prevalencia y pronóstico a largo plazo de anormalidades en niveles de anticuerpos IgG contra HP (HP-IgG) en pacientes con SCA.

**Material y métodos**

La población estuvo constituida por 67 sujetos consecutivos hospitalizados por SCA (angina inestable [AI]/infarto agudo de miocardio [IAM]) dentro de las 24 horas del inicio de los síntomas, entre abril de 2003 y diciembre de 2003, quienes fueron evaluados mediante un kit inmunoenzimático comercial (Meridian Diagnostics, USA).

**Resultados**

Durante el seguimiento (12 ± 3 meses) se registraron 10 (14,6%) eventos (muerte/infarto/rehospitalización por AI). El área bajo la curva ROC de HP-IgG para predecir eventos fuede 0,85 ± 0,06 (IC 95% 0,74-0,96); el punto de corte de 185 UI mostró una sensibilidad del 70% y una especificidad del 82%. Según el nivel de HP-IgG por encima o por debajo de 185 UI, los pacientes se dividieron en grupo 1 (25,4%) y grupo 2. Ambos fueron comparables. La supervivencia anual libre de eventos fue del 67% versus el 90% en los grupos 1 y 2, respectivamente (prueba de rangos logarítmicos, p = 0,01). Al ingreso, un nivel de HP-IgG > 185 UI (hazard ratio [HR] = 5,588; p = 0,039), la hipotensión arterial (HR = 1,109; p = 0,035) y niveles elevados de creatinina (HR = 1,997; p = 0,019) fueron predictores independientes de eventos.

**Conclusiones**

En uno de cada cuatro pacientes con SCA se detectaron tempranamente niveles elevados de HP-IgG. Títulos mayores de 185 UI se asociaron con peor evolución a largo plazo.

**Palabras clave >** Síndrome coronario agudo - *Helicobacter pylori* - Pronóstico

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