Seroprevalence of *Helicobacter pylori*/CagA Antibodies in Guatemalan Gastric Cancer Patients: Association of Seropositivity with Increased Plasma Levels of Pepsinogens but not Soluble Urokinase Plasminogen Activator Receptor

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Abstract. Infection by *Helicobacter pylori* is a major risk factor for gastric cancer (GC), the second leading cause of cancer-related death worldwide. Although biomarkers such as pepsinogens (PGs) and soluble urokinase plasminogen activator receptor (suPAR) may have diagnostic and/or prognostic value in patients with GC, their levels may be affected by *H. pylori* infection. The aim of this study was to investigate the association of the presence of antibodies to *H. pylori* and cytotoxin-associated gene A (CagA) with plasma levels of PGs and suPAR in a cohort of Guatemalan GC patients and controls. To this end, levels of suPAR, Pepsinogens I and II (PGI and PGII), and antibodies to *H. pylori* and CagA toxin were determined by ELISA in plasma samples from 67 GC patients and 136 matched healthy controls. Seropositivity for CagA was significantly higher in patients with GC than in controls. Pepsinogens II and suPAR levels were higher and PGI/PGII ratios were lower in GC patients than in controls. There was a significant association of *H. pylori* seropositivity status with increased levels of PGII and lower PGI/PGII ratios, particularly in the control (non-GC) population. The levels of suPAR were not significantly affected by *H. pylori* or CagA seropositivity status. These results suggest that the seropositivity status for *H. pylori* and CagA need to be taken into account during the GC diagnostic process.

INTRODUCTION

Gastric cancer (GC) is the most common neoplasia of the gastrointestinal (GI) tract and the fifth most common type of cancer in the world, with a frequency that varies greatly depending on the geographic location, with some of the highest risk areas located in Asia, particularly Japan, Korea, and China, as well as in some Latin American countries.[1–3] In Guatemala, GC presents some of the highest rates of incidence and mortality in the world and occupies the fourth place among the most common cancers for both genders.[2,4] The risk of GC is slightly higher for males and affected by a number of other factors, including genetics, weight, diet, and socioeconomic level.[5,6] However, the most significant risk factor appears to be infection by *Helicobacter pylori*, a Gram-negative bacteria adapted to the stomach microenvironment that has the ability to invade the gastric mucosa and cause inflammation, leading to gastritis, ulcers, and neoplasia.[5,7] Although 85% of people infected do not develop symptoms, those who do are often infected by pathogenic strains of *H. pylori.* Such strains carry a pathogenicity island in their genomes encoding cytotoxin-associated gene A (CagA), a major virulence factor whose presence has been directly associated with ulcer-causing *H. pylori* strains.[8–10] *Helicobacter pylori* strains producing CagA are more likely to cause tissue damage and inflammation than those that lack their production, and thus more likely to be associated with GC.[11,12]

There has been a lot of interest in the identification of diagnostic and prognostic biomarkers for GC. Among some of the markers receiving the most attention are the plasma levels of pepsinogens (PGs). Pepsinogens I and II (PGI and PGII) are two biochemically and immunologically distinct proenzymes

of pepsin with different patterns of expression in the stomach. Whereas PGI is mainly expressed by chief cells in the fundus, PGII is distributed throughout the gastric mucosa and the proximal duodenum.[13,14] The levels of PGI and PGI/PGII ratios in serum correlate with morphological and functional changes in the gastric mucosa and have been proposed as markers of atrophic gastritis and GC.[15–20] However, although relatively useful, PG tests may have limitations that affect their sensitivity and specificity for the detection of GC. In addition to several demographic and pathologic factors, PG tests have been reported to be affected by *H. pylori* infection.[5–7,21]

Another potentially important biomarker associated with a number of malignancies, including GC, is the urokinase plasminogen activator receptor (uPAR or CD87).[22–24] As a regulator of fibrinolysis through the binding and activation of urokinase plasminogen activator, uPAR is associated with degradation of the extracellular matrix and basement membranes, important factors in tumor cell invasion, and metastasis.[23–26] Soluble urokinase plasminogen activator receptor (suPAR) may be generated by several mechanisms, including cleavage of the GPI anchor by phospholipases, cleavage by proteolytic enzymes, and alternative mRNA splicing.[27–30] Both membrane and soluble forms of uPAR have been reported in neoplastic cell lines and in several types of in vivo malignancies, including gastric, colon, breast, and lung cancers.[22,31,32] Increased uPAR expression in tumor tissue has been correlated with a poor prognosis, and elevated levels of suPAR have been reported in the sera of patients with GC as well as other cancers, suggesting a potential use as a diagnostic/prognostic biomarker.[31,33–37] Although *H. pylori* infection has been reported to promote uPAR expression in gastric epithelial and gastric carcinoma cells,[10,38] the effect on the plasma levels of suPAR levels has not been studied.

The purpose of this study was to determine the seroprevalence of *H. pylori* and CagA antibodies in a cohort of Guatemalan GC patients and controls and to investigate

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whether the seropositivity status affects the plasma levels of PGs and suPAR.

MATERIALS AND METHODS

Study design and subjects. Sixty-seven patients who were diagnosed with gastric adenocarcinoma and 136 age- and gender-matched healthy controls were included in the study. Most patients and controls self-identified as "Ladino" or "indigenous," the two main ethno-cultural groups recognized in Guatemala (the Guatemalan population is roughly 60% Ladino or mestizo and 40% indigenous or Mayan, with a low percentage of other groups). Subjects were recruited after understanding and signing written consent from the Institute of Cancerology (*Instituto de Cancerología—INCAN*), the Roosevelt Hospital, the Center for Biomedical Research (Centro de Investigaciones Biomédicas) of the Universidad San Carlos de Guatemala, and the Gastro-Centro, all in Guatemala City, Guatemala, between February and September 2015. The study was reviewed and approved by the Institutional Review Boards from the aforementioned institutions and conformed with the Code of Ethics of the World Medical Association (Declaration of Helsinki), printed in the *British Medical Journal* (July 18, 1964).

Inclusion criteria. *Cancer group.* The group included patients aged 18 years or older with a diagnosis of distal or proximal gastric adenocarcinoma based on endoscopy and histopathologic analysis of a gastric biopsy.

Control group. The group included healthy subjects aged 18 years or older willing to participate in the study. Subjects were recruited from asymptomatic and non-oncologic patients attending ambulatory care gastroenterology clinics at the Institute of Cancerology and the Roosevelt Hospital or from persons undergoing routine laboratory tests at the Center for Biomedical Research of the Universidad San Carlos de Guatemala.

Exclusion criteria. *Cancer group.* The group included patients previously operated for GC or with metastatic tumors originating in other organs and treated for mucosa-associated lymphoid tissue (MALT) lymphoma or any other gastric disease besides gastric adenocarcinoma. Patients previously treated with chemotherapy and/or radiotherapy and/or diagnosed with autoimmune pathologies were also included.

Control group. The group included subjects with a history of malignancy of any type, treated for gastric disease and/or previously diagnosed with autoimmune pathologies.

Diagnosis. The diagnosis of the gastric adenocarcinoma cases was based on an upper GI endoscopy procedure and histopathologic analysis of a gastric biopsy. Data were collected for each cancer case on the macroscopic (Borrmann classification[39]) and microscopic/histologic features of the tumors (Lauren classification[40]), the number of affected sites, and localization in the stomach.

Samples. Fasting venous blood samples from controls and cancer patients were obtained using K_2EDTA vacutainer tubes before GC treatment. Samples were maintained at 4°C and processed within 1 hour of collection. The tubes were centrifuged at $500 \times g$ for 10 minutes, and the plasma was removed by aspiration and aliquoted. Plasma samples were then stored at −70°C, until assayed.

***Helicobacter pylori* serology.** Serum antibodies to *H. pylori* were measured using a qualitative ELISA based on a modification of a previously described method.[41] Briefly, antigen was prepared by sonicating five different strains of *H. pylori* isolated from patients in Costa Rica. ELISA plates (Immulon 2HB, Thermo Scientific, Waltham, MA) were coated with 100 µL of the antigen preparation (100 ng/mL in carbonate buffer, pH 9.6) by overnight incubation at room temperature followed by blocking with 250 µL of 0.1% gelatin in phosphate-buffered saline (PBS) for 3 hours. Serum samples and negative internal controls (diluted 1:800 in PBS containing 0.1% gelatin and 0.5% bovine gamma globulin [Sigma, St. Louis, MO]) were added to the wells and incubated at 37°C for 60 minutes. Positive internal controls were also included but diluted 1:7,500. After washing, the wells were incubated for 1 hour at 37°C with a goat anti–antihuman IgG antibody conjugated with alkaline phosphatase (Biosource International). Detection was performed by the addition of substrate (Fast p-Nitrophenyl Phosphate Tablet Sets, Sigma-Aldrich, St. Louis, MO) and reading at 405 nm. A sample was considered positive when the net absorbance of the serum was higher or equal to 0.75 of the average positive control. Each sample was assayed three times, and sera were considered positive when at least two of the three tests resulted positive. Validation of the ELISA was previously performed using 230 sera from persons with known *H. pylori* status as determined by the urea breath test (Ballard Medical Products, Draper, UT). The positive and negative predictive values were 96% and 90%, respectively.

Cytotoxin-associated gene A serology. Serum antibodies to CagA were measured using a modified version of the ELISA described by Blaser et al.[42] Briefly, ELISA plates coated with purified recombinant CagA antigen were incubated with serum samples and controls, all diluted (1:100). The subsequent steps were identical to those performed for the *H. Pylori* serology described in the previous section. The CagA ELISA has been validated comparing serum samples from subjects confirmed to be infected or not infected with CagA-positive strains of *H. pylori*. The optimal cutoff point was at 0.3 of the average positive control.

Soluble urokinase plasminogen activator receptor and pepsinogen assays. Levels of suPAR in plasma were quantified using commercial ELISA kits (Human uPAR Immunoassay, R&D Systems, Minneapolis, MN) according to the manufacturer's instructions.

Levels of pepsinogens I and II (PGI and PGII) in plasma were assayed using ELISA methodology (Biohit Oyj, Finland). The PGI/PGII ratio was calculated by dividing the corresponding concentrations of the two PGs.

Statistics. Sample size was established following a power analysis using the EPIDAT program and a moderate effect size ($d = 0.5$) based on previously published data on suPAR levels, a sample ratio of 2.0, a confidence level of 95%, and a power of 90%. Initially, the Shapiro–Wilk test was used to determine whether the data were normally distributed. The Chi-square test was used to analyze differences in the positivity rate for the serological markers and effects of ethnicity. Because of non-normal distribution, the Wilcoxon–Mann–Whitney test was used to compare the levels of suPAR, PGs, and PGI/PGII ratios between the two groups and to compare data for the two microscopic tumor types. Point biserial correlation analysis was used to analyze the correlation between the biomarkers and positivity for *H. pylori* and CagA antibodies. Statistical analyses were performed using SAS® 9.4 (SAS Institute, Cary, NC). *P*-values of < 0.05 were considered statistically significant.

TABLE 1
Subject groups—demographical and serological characteristics

Variable	Control group (n = 136)	Cancer group (n = 67)	P-value
Gender			
Female	60 (44.1%)	30 (44.8%)	
Male	76 (55.9%)	37 (55.2%)	
Age (years), mean ± SD	58.5 ± 12.6	59.5 ± 13.0	0.630
Ethnicity			
Ladino	118 (86.8%)	48 (71.6%)	
Indigenous	17 (12.5%)	18 (26.9%)	
Other	1 (0.7%)	1 (1.5%)	
Serology			
H. pylori (positive)	64 (45.5%)	34 (50.8%)	0.522
CagA (positive)	75 (53.2%)	49 (73.1%)	0.007*

H. pylori = Helicobacter pylori.
* P < 0.001.

RESULTS

Demographic data. Table 1 shows the demographic and serologic characteristics of the cancer and control groups. Both of them were composed of approximately 44% females and 56% males, respectively. The average age of the cancer group (59.5 years) was not significantly different from that of the control group (58.5 years; $P = 0.630$). Breakdown by ethno-cultural groups indicated a composition of 70.6% Ladino, 27.9% indigenous, and 1.5% other for the cancer group, and 86.8% Ladino, 12.5% indigenous, and 0.7% other for the control group. The seropositivity rates for H. pylori between the control and cancer groups (45.5 versus 50.8%, respectively; $P = 0.522$) were not significantly different. However, the prevalence of anti-CagA antibodies was found to be significantly higher in patients with GC than in controls (73.1 versus 53.2%, respectively; $P = 0.007$; odds ratio = 2.396).

Gastric cancer case characteristics. Table 2 summarizes the characteristics of the GC cases. Macroscopically, the most common presentation was type III (ulcerative with indistinct borders) of the Borrmann classification (72%), followed by types I (polypoid fungating) and IV (diffuse, indistinct borders) with 12% and 11% of the cases, respectively. Microscopically, most of the tumors were diagnosed as either intestinal (55%) or diffuse (42%), with the remaining 3% being mixed, according to the Lauren classification. In terms of localization in the stomach, the body and the antrum were the most common sites (46% and 37%, respectively), followed by the fundus (15%) and pylorus (3%). The GC group comprised patients at all clinical stages, including stages I (7.5%), II (40.3%), III (22.4%), and IV (28.4%).

Ethnicity and differences in microbiological markers and microscopic tumor types. Comparisons of the prevalence of antibodies to H. pylori and CagA as well as that of the two main microscopic tumor types between the two main Guatemalan ethnic groups are shown in Table 3. There were no statistically significant differences in the seropositivity rates for H. pylori between the Ladino and indigenous populations, and although the latter population showed a moderately higher seropositivity rate for CagA, the difference with the Ladino population (71.4 versus 57.2%, respectively) was not statistically significant. Although the distributions of intestinal versus diffuse GC types in the Ladino and indigenous groups were almost reversed, with the intestinal type being more prevalent in the former and the diffuse type in the latter

TABLE 2
Gastric cancer case characteristics

Variable	Number (%) (n = 67)
Tumor type (macroscopic—Borrmann classification~)	
Type I (polypoid and fungating)	8 (11.9)
Type II (ulcerative with elevated distinct borders)	4 (6.0)
Type III (ulcerative with indistinct borders)	48 (71.6)
Type IV (diffuse and indistinct borders)	7 (10.5)
Tumor type (microscopic—Lauren classification)	
Intestinal	37 (55.2)
Diffuse	28 (41.8)
Mixed	2 (3.0)
Anatomical localization*	
Cardia	0 (0)
Fundus	10 (14.9)
Body	30 (44.8)
Antrum	25 (37.3)
Pylorus	2 (3.0)
Clinical stage	
I	5 (7.5)
II	27 (40.3)
III	15 (22.4)
IV	19 (28.4)
Undetermined	1 (1.5)

* For those cases with two or more sites, the primary localization was considered.

group (about two-thirds in each case), the differences were not statistically significant. There were no statistically significant differences in the seropositivity for H. pylori or CagA antibodies when comparing individuals with intestinal versus diffuse tumors (results not shown).

Biochemical markers: Levels of PGs and suPAR in cancer and control groups. Results of the determinations of plasma PGI, PGII, and PGI/PGII ratios and suPAR levels in the cancer and control groups are shown in Table 4. Analysis of pepsinogen levels indicated that although there was no statistically significant difference in the levels of PGI between the two groups, the levels of PGII were significantly higher in the cancer than in the control group. There was also a significant difference between the two groups in PGI/PGII ratios: these being lower in the cancer group. The cancer group had significantly higher levels of suPAR than the controls ($P < 0.0001$).

Correlation between serological and biochemical markers. Table 5 shows the association between seropositivity for anti–H. pylori or CagA antibodies with the levels of the biochemical markers. Because of the potential confounding effect of the presence of GC, these studies analyzed data from the control and cancer groups separately. The comparison of median biomarker levels of H. pylori–seronegative versus seropositive individuals in the control group suggested that the levels of both PGs, but particularly PGII, were higher in the seropositive individuals, whereas PGI/PGII ratios were lower. These effects were not as evident in the cancer group, with exception of smaller effect on PGII levels. A point biserial correlation analysis showed a moderate positive correlation between seropositivity for H. pylori and the levels of PGII and a negative correlation with the PGI/PGII ratios in the control group. The comparison of CagA-seronegative versus seropositive individuals showed significantly higher levels of PGII in seropositive individuals in both the control and cancer groups as well as lower PGI/PGII ratios in the latter. The plasma levels of suPAR were not affected by H. pylori or CagA status in either group.

Variable	Ladino, n (%)	Indigenous, n (%)	*P*-value
Serology*			
H. pylori (positive)	80 (48.2)	19 (54.3)	0.512
CagA (positive)	95 (57.2)	25 (71.4)	0.120
Tumor type (Lauren classification)†			
Intestinal	31 (64.6)	7 (38.9)	
Diffuse	17 (35.4)	11 (61.1)	0.060

H. pylori = Helicobacter pylori.
* Serology (Ladino, n = 166; indigenous, n = 35).
† Tumor type (Ladino, n = 48; indigenous, n = 18).

TABLE 4
Biomarker levels

Variable	Control group (n = 136)	Cancer group (n = 67)	*P*-value
PGI (ng/mL)	149.0 (95.9)	124.2 (150.3)	0.455
PGII (ng/mL)	12.6 (11.4)	20.4 (16.3)	0.003*
PGI/PGII ratio	10.9 (7.9)	7.4 (5.3)	< 0.0001*
suPAR (ng/mL)	2.01 (0.85)	3.15 (2.73)	< 0.0001*

Pepsinogens I = PGI; Pepsinogens II = PGII; suPAR = soluble urokinase plasminogen activator receptor. Values represent median (IQR).
* P < 0.01.

DISCUSSION

The main objective of this study was to evaluate the association of seropositivity status for antibodies to *H. pylori* and CagA with the levels of PGI, PGII, and their ratios (biochemical markers associated with the presence of atrophy and GC) as well as those of suPAR in a cohort of Guatemalan GC patients and controls. Serologic analysis indicated that there were no statistically significant differences in the seropositivity for *H. pylori* in GC patients and controls, accounting for approximately half of the population in each group, a seropositivity rate that is in line with previous studies in the Guatemalan population.[43,44] However, seropositivity for anti-CagA antibodies was significantly higher in patients with GC (P = 0.007), confirming that infection with pathogenic strains of *H. pylori* is an important risk factor for GC. The finding of individuals from both groups who were positive for CagA but negative for *H. pylori* antibodies [*H. pylori* (–)/CagA (+)] was not totally unexpected, as this has been previously reported by other studies and attributed to insufficiently high levels of antibodies to the *H. pylori* antigens used in the ELISA.[11] We also found *H. pylori* (+)/CagA (–) individuals in both the GC (4.4%) and control groups (10.3%). These individuals might represent infections with *H. pylori* CagA strains. We also compared the *H. pylori* (+)/CagA (–) individuals *with H. pylori* (–)/CagA (+) and *H. pylori* (+)/CagA(+) individuals in terms of their biomarkers (PGI, PGII, and PGI/PGII ratios and suPAR levels), but found no statistically significant differences. However, *H. pylori* (+)/CagA (+) individuals in the control group had significantly higher median levels of PGII (18.4 versus 8.4 ng/mL; P < 0.001) and lower PGI/PGII ratios (7.8 versus 12.8; P < 0.001) than those that were *H. pylori* (–)/CagA (+), suggesting that individuals who are seropositive for both *H. pylori* and CagA are more likely to have higher levels of PGII and lower PGI/PGII ratios than those positive for CagA only. One plausible interpretation is that seroconversion for CagA antibodies might be more sensitive and require a smaller bacterial exposure than seroconversion for *H. pylori* antibodies, as measured by the current ELISA tests. The latter may require a more substantial exposure or infection with the bacteria and, thus, might better correlate clinically with gastric mucosal inflammation and the observed elevated levels of PGII and lower PGI/PGII ratios.

Investigation of whether GC cases in Guatemala differ among ethno-cultural divisions showed no statistically significant differences. However, we observed that the patterns of distribution of the two main microscopic GC types (intestinal versus diffuse) were almost opposite in the Ladino versus indigenous population, with the intestinal type accounting for almost two-thirds of the GC cases in the former and the diffuse type for two-thirds in the latter population. Although not statistically significant, these results are provocative and call for a more extensive investigation.

Our studies found that PGI/PGII ratios were significantly lower in patients with GC than in controls. The lower PGI/PGII ratios in our study appeared to be a consequence of higher levels of PGII in the cancer group than in the controls because the levels of PGI were not significantly different between the two groups. Increased PGII levels and lower PGI/PGII ratios have been reported to be major risk factors for gastric ulcers by Samloff and others.[45] Elevated serum PGII levels have also been associated with infiltration of the gastric mucosa by neutrophils and monocytes as a result of *H. pylori* infection.[46] Indeed, our studies found that even individuals without GC who were seropositive for *H. pylori* or CagA antibodies had higher levels of plasma PGII (as well as lower PGI/PGII ratios) than seronegative individuals. Such findings suggest the importance of taking into account the serological status for *H. pylori* when evaluating PG levels in patients at risk of GC.

Our group recently reported the presence of higher levels of plasma suPAR in a cohort of Guatemalan patients with GC,[47] consistent with previous studies reporting elevated suPAR levels in patients GC and other types of cancer.[22,24,35–37] Although some of these studies have also reported a prognostic value for suPAR tests, with higher levels being associated with reduced survival,[31,35–37] the mechanisms underlying the increased suPAR levels in patients with cancer are not yet clear. High levels of uPAR expression have not only been demonstrated in malignant cells but also in stromal cells, such as macrophages, neutrophils, and endothelial cells.[48,49] Thus, elevated suPAR levels could probably reflect both enhanced tissue remodeling and inflammation.[24,31] Taking into account that suPAR levels are not specific for any particular type of cancer, these characteristics would be consistent with suPAR levels being a better prognostic rather than diagnostic marker. From the point of view of pathogenic mechanisms and based on the biological roles of uPAR, including plasmin activation and matrix degradation as well as activation of signaling pathways leading to alterations in cell adhesion and motility, high uPAR expression in the tumor microenvironment may endow malignant cells with a clear advantage in terms of tissue invasion, angiogenesis, and metastasis.[21,25,30] Despite reports that *H. pylori* infection of gastric epithelial and gastric carcinoma cells promoted uPAR expression in these cells,[9,38] our studies found that plasma suPAR levels were not affected by seropositivity rates for *H. pylori* or CagA, suggesting that the use of suPAR levels as a potential GC marker may not be complicated by previous *H. pylori* infection.

This study has several limitations. Our control population included only age- and gender-matched, healthy individuals.

TABLE 5
Association of *H. pylori* and CagA seropositivity with biochemical markers

Biochemical marker	*H. pylori* negative	*H. pylori* positive	*P*-value	Point biserial correlation rbp (*P*-value)
Control group				
PGI (ng/mL)	112.9 (99.2)	164.5 (68.8)	0.001**	0.237 (0.006)*
PGII (ng/mL)	8.2 (6.6)	17.8 (11.0)	< 0.0001**	0.383 (< 0.0001)**
PGI/PGII ratio	13.1 (8.5)	8.4 (6.1)	< 0.0001**	−0.337 (< 0.0001)**
suPAR (ng/mL)	1.92 (1.04)	2.01 (0.69)	0.517	−0.103 (0.235)
Cancer group				
PGI (U/mL)	117.6 (170.1)	118.3 (128.5)	0.430	0.028 (0.823)
PGII (U/mL)	14.5 (17.7)	22.3 (15.5)	0.044*	0.099 (0.433)
PGI/PGII ratio	9.3 (8.4)	6.4 (4.7)	0.069	−0.250 (0.045)*
suPAR (ng/mL)	3.66 (2.49)	2.51 (3.01)	0.099	−0.083 (0.516)
	CagA neg.	CagA pos.		
Control group				
PGI (U/mL)	136.7 (95.9)	154.9 (94.2)	0.080	0.124 (0.152)
PGII (U/mL)	9.0 (9.7)	15.3 (10.8)	0.001**	0.148 (0.086)
PGI/PGII ratio	12.3 (8.2)	9.8 (6.2)	0.063	−0.152 (0.077)
suPAR (ng/mL)	1.92 (0.90)	2.02 (0.82)	0.418	0.063 (0.467)
Cancer group				
PGI (U/mL)	124.2 (188.8)	118.3 (136.5)	0.532	0.101 (0.421)
PGII (U/mL)	11.6 (16.7)	21.8 (17.1)	0.036*	0.244 (0.048)*
PGI/PGII ratio	11.1 (9.7)	6.4 (4.9)	0.030*	−0.291 (0.018)*
suPAR (ng/mL)	3.86 (4.12)	2.91 (2.58)	0.403	−0.095 (0.450)

H. pylori = *Helicobacter pylori*; CagA = cytotoxin-associated gene A; Pepsinogens I = PGI; Pepsinogens II = PGII; suPAR = soluble urokinase plasminogen activator receptor. Values represent median (IQR).
* $P < 0.05$.
** $P < 0.01$.

Because suPAR levels may also be elevated in other cancers and even in cases when there is systemic inflammation, they alone should not be taken as specific for GC. It is also not clear how premalignant gastric pathologies (e.g., atrophic gastritis) may affect suPAR levels, and thus, additional studies need to be undertaken to evaluate patients with such conditions.

In conclusion, our studies demonstrated that in the Guatemalan population studied, the presence of GC was significantly associated with seropositivity for CagA antibodies. The levels of PGII and suPAR were found to be higher and PGI/PGII ratios lower in GC patients than in controls. However, a significant association was found between *H. pylori* seropositivity and increased levels of PGII and lower PGI/PGII ratios, even in the control (non-GC) population. By contrast, the levels of suPAR were not affected. These results suggest that the seropositivity status for *H. pylori* and CagA need to be taken into account during the GC diagnosis workup.

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