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Gender, age, endoscopic findings, urease and *Helicobacter pylori*: all uncorrelated within a sample of a high gastric cancer prevalence population in Amazon

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ABSTRACT – **Background** – It is widely assumed that gender, age, gastritis and *Helicobacter pylori*, all have some degree of correlation and, therefore, can synergistically lead to the development of gastric cancer. **Objective** – In this cross-sectional study, we expected to observe the above mentioned correlation in the analysis of medical records of 67 patients of both sexes (female, n=44), mean age ± standard deviation: 41±12 years old, all from Belém (capital of Pará State, Brazilian Amazon), a city historically known as one with the highest gastric cancer prevalence in this country. **Methods** – All patients were submitted to upper gastrointestinal endoscopy for gastric biopsy histopathological analysis and rapid urease test. All diagnoses of gastritis were recorded considering its topography, category and the degree of inflammatory activity, being associated or not associated with *H. pylori* infection. **Results** – The results show that no statistically relevant associations were found among the prevalences of the observed variables. **Conclusion** – The authors hypothesize that observed risk factors associated to gastric cancer might be lesser synergistic than is usually expected.

HEADINGS – Stomach neoplasms. Gastrointestinal endoscopy. Sex characteristics. Age factors. Analysis of variance. Urease. *Helicobacter pylori*.

INTRODUCTION

The historical distribution of gastric cancer in Brazil shows that it is highly prevalent in Pará State (northern Brazil). Mortality due to gastric cancer in Belém, the capital city of Pará, was 27.1/100,000 inhabitants in 1982, decreasing to 15.0/100,000 inhabitants in 1997. In this period, mortality reduction was important in males and in the age group over 60 years. However, mortality rates due to gastric cancer in this city were always higher than those registered in most Brazilian capitals. Currently, estimates for the biennium 2018-2019 made by the National Cancer Institute (INCA) show that gastric cancer might be the second most frequent in men (12.35/100,000 inhabitants), and the fifth most frequent in women (5.34/100,000 inhabitants), in North Region of this country[1-3].

Epidemiological studies have shown that areas with high gastric cancer rates often have a correspondingly high prevalence of *Helicobacter pylori* infection. It is widely assumed that *H. pylori* can induce chronic active gastritis, both of which, in turn, can lead to the development of gastric cancer. Indeed, a high incidence of *H. pylori* infection was found recently in a cross-sectional study with 554 patients from Belém, mainly among patients with gastric ulcer and gastric cancer[4].

Thus, gastric cancer prevention demands an accurate detection of *H. pylori*-associated gastritis[5]. Among commonly used tests to detect *H. pylori* are the histological examination of gastric biopsies and rapid urease test, being the former the gold standard. Rapid urease tests (RUT) also use biopsies to detect gastric urease, considered a biomarker for the presence of *H. pylori*. Five biopsy specimens from different stomach sites should be collected to perform histological examination and, therefore, RUT, according to the updated Sydney Classification, which had set the gold standard for gastric biopsy[6-8]. However, this recommended approach is uncommon in medical daily practice in Brazil.

In addition to *H. pylori*-associated gastritis profile and patients gender, many other risk or protective factors are associated to gastric cancer in the literature. For instance, aging and gender-related hormonal profile. While both gastric mucosa barrier and acid concentration seems to decrease with age and earlier in *H. pylori* infected patients[9], prevalence of *H. pylori* infection, prevalence of gastritis with atrophy, and incidence of gastric cancer, all seems to increase with age[10]. On the other hand, hormonal profile in females is hypothesized as playing as a protective factor that might explain the difference in incidence rates of gastric cancer among females and males[11].

In this broad and complex context, an important issue yet remains to be clarified: if these factors act synergistically toward gastric cancer, and how. Much of the above-mentioned literature suggests this alternative. However, evidence against also can be

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found. For instance, in Saudi Arabia, where incidence rate of *H. pylori* infection in chronic gastritis ranges between 50%–96%, no significant association between infection rate and aging was found, while men and women were equally affected by the infection[12].

Thus, the present cross-sectional study aimed to verify the degree of association among above-mentioned risk factors (e.g. gender, age, endoscopic findings, urease and *H. pylori*) within a sample of a high gastric cancer prevalence population (Belém, Pará, Brazil). Surprinsingly, no statistically relevant associations were found among the observed variables. The authors hypothesize that observed risk factors associated to gastric cancer might be lesser synergistic than is usually expected.

METHODS

The sample studied was composed of 100 medical records of patients attended, in 2016, in a private gastroenterology clinic (convenience sampling). Of these records, two were discarded for being patients without a diagnosis of gastritis. Of the remaining ninety-eight, 31 were discarded because they did not have a record of the histopathological findings. Thus, the present cross-sectional study was performed with data obtained from 67 records of unidentified patients of both sexes (44 women), mean age at 41±12 years. All patients were from the city of Belém (Pará, Brazil), and underwent upper digestive endoscopy and gastric biopsy to perform RUT and histopathological examination for *H. pylori* detection.

One-way Analysis of Variance (ANOVA) and unpaired *t*-test were used to analyze the difference between mean age values, and F test was used to compare variance in age values of patient's groups when it was necessary to verify the extent of a potential statistical difference (a=0.05, with 95% confidence interval [95% CI] of all *P*-values). In addition, prevalence of variables (with 95% CI) and Fisher's exact test (a=0.05, with 95% CI of all *P*-values) were used to compare proportions observed in the sample under study, e.g. analyze the chance that convenience sampling would result in an association as strong (or stronger) as observed among variables prevalences. All data analyses were performed using GraphPad Prism version 8.00 for Mac (GraphPad Software, La Jolla, California USA, www.graphpad.com).

The Research Ethics Committee of the Tropical Medicine Nucleus, Federal University of Pará, and the National Research Ethics Committee (CONEP), both approved this work (Report: 576.418).

RESULTS

In FIGURE 1, we compare the mean age (± standard deviation) of male and female patients (1A), of patients with pangastritis (PAN), body (BOD) and antrum (ANT) gastritis (1B), of patients with mild (MILD) and moderate (MOD) gastritis (1C), of patients with positive [hp(+)] and negative [hp(-)] histopathological results for *H. pylori* (1D), and of patients with erythematous (ER) and enanthematous (EN) gastritis (1E). No statistical relevant differences were found (see TABLE 1).

It is worth noting that FIGURE 1F shows a statistical difference between the mean ages of the EN and ER groups shown in FIGURE 1E (95% CI of the difference between EN and ER means: -20.012 to -2.96; unpaired *t* test: *P*=0.009, 95% CI of *P*: 0.032 to 0.000). However, this statistical difference was small in magnitude (~3 years). In addition, no statistical relevant difference was found among variances of EN and ER groups (F test, *P*=0.22, 95% CI of *P*: 0.122 to 0.321; see TABLE 1).

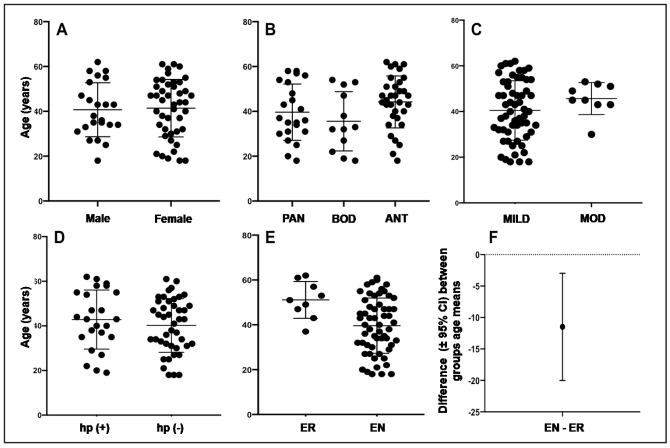

FIGURE 1. Comparison between ages (mean ± standard deviation) of patients in the sample studied, considering variables gender (A), topography of gastritis (B), degree of inflammatory activity in gastritis (C), histopathological results for *H. pylori* (D), and category of gastritis (E). No statistical relevant differences were found (see TABLE 1 and text). PAN, pangastritis; BOD, body gastritis; ANT, antral gastritits; MILD, mild gastritits; MOD, moderate gastritis; hp(+), positive histopathological results for *H. pylori*; hp(-), negative histopathological results for *H. pylori*; ER: erythematous gastritis; EN: enanthematous gastritis.

TABLE 1. Statistical measures of the size of differences among patients' mean ages in the sample studied, considering the variables shown in FIGURE 1.

	Difference between age means ($CI_{95\%}$)	One-way ANOVA (*P* value [$CI_{95\%}$])	
PAN – BOD*	4.053 (-5.29–13.396)		
PAN – ANT	-4.575 (-11.184–2.032)	0.093 [0.163–0.024]	
BOD – ANT	-8.628 (-16.8– -0.457)		
	Difference between age means ($CI_{95\%}$)	**Unpaired *t* test (*P* value [$CI_{95\%}$])**	**F test (*P* value [$CI_{95\%}$])**
Male – Female	0.713 (-5.73–7.16)	0.825 [0.735–0.917]	–
MILD – MOD	5.201 (-3.69–14.092)	0.247 [0.144–0.35]	–
hp (+) – hp (-)	2.6 (-3.756–8.958)	0.416 [0.299–0.535]	–
EN – ER	-11.49 (-20.012– -2.968)	0.009 [0.0–0.032]	0.221 [0.122–0.321]

*All abbreviations are as in FIGURE 1. (-), when was not necessary apply F test.

In FIGURE 2, we compare the prevalences (±95% CI) of male and female patients with hp(+) and hp(-) (2A), with PAN and BOD/ANT gastritis (2B), with EN and ER gastritis (2C), and with MILD and MOD gastritis (2D). FIGURE 2A shows that the prevalence of hp(-) in female is statistically higher than the other observed prevalences. However, this statistical difference was small in magnitude [~1.4% among hp(+) and hp(-) results in female, and ~3% among hp(-) results in male and female]. In addition, no statistical relevant associations were found between the prevalences of histopatological results for *H. pylori* and patients' gender (Fisher's exact test, *P*=0.424, 95% CI of *P*: 0.306 to 0.542; see TABLE 2).

In FIGURE 2B, it is observed that the prevalence of BOD/ANT in female is statistically higher than the other prevalences observed. However, no statistical relevant associations were found between the prevalences of gastritis topography and patients' gender (Fisher's exact test, *P*=0.098, 95% CI of *P*: 0.027 to 0.17; see TABLE 2).

In FIGURE 2C, it is worth noting that the prevalence of EN in male and female is statistically higher than the prevalence of ER. However, no statistical relevant associations were found between the prevalences of gastritis category and patients' gender (Fisher's exact test, *P*=0.48, 95% CI of *P*: 0.36 to 0.6). Similarly, FIGURE 2D shows that the prevalence of MILD in male and female is statistically higher than the prevalence of MOD. However, no statistical relevant associations were found between the prevalences of MILD, MOD and patients' gender (Fisher's exact test, *P*=0.48, 95% CI of *P*: 0.36 to 0.6; see TABLE 2).

In FIGURE 3, we compare the prevalences (±95% CI) of *H. pylori* infected and non-infected patients with positive (U+) and negative (U-) results in RUT (3A), with PAN and BOD/ANT gastritis (3B), with EN and ER gastritis (3C), and with MILD and MOD gastritis (3D). No relevant statistical association was found (see TABLE 3). For instance, FIGURE 3A shows that no

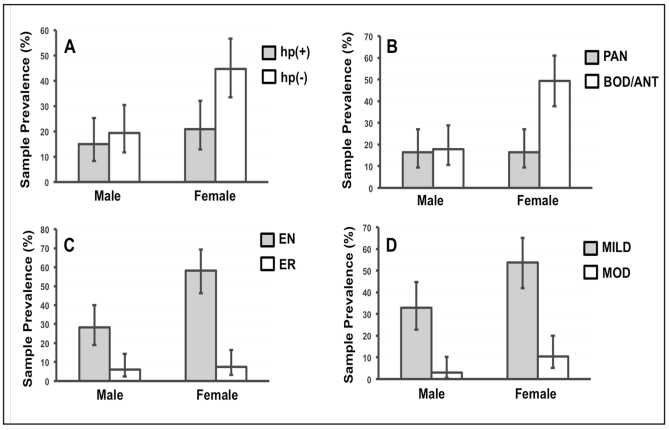

FIGURE 2. Comparison between prevalences (±95% CI) of male and female patients with positive and negative histopathological results for *H. pylori* (A), with pangastritis and body/antrum gastritis (B), with enanthematous and erythematous gastritis (C), and with mild and moderate gastritis (D). No statistical relevant association was found (see TABLE 2 and text). Abbreviations are as in FIGURE 1.

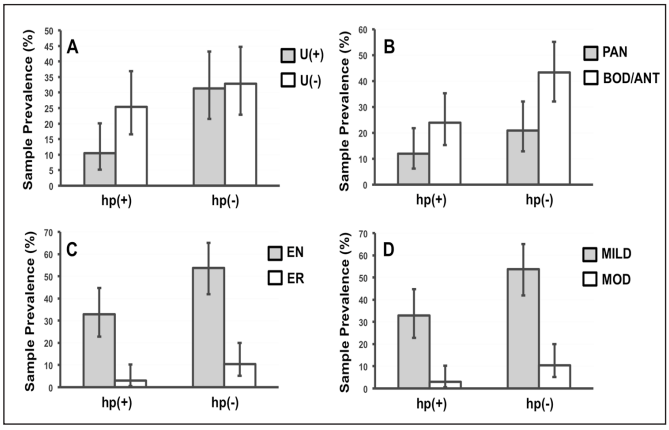

FIGURE 3. Comparison between prevalences (±95% CI) of *H. pylori* infected and non-infected patients with positive and negative results in RUT (A), with pangastritis and body/antrum gastritis (B), with enanthematous and erythematous gastritis (C), and with mild and moderate gastritis (D). No relevant statistical association was found (see TABLE 3 and text). Abbreviations are as in FIGURE 1.

TABLE 2. Statistical measures of the degree of association between prevalences of gender and gastritis-associated variables shown in FIGURE 2.

Gender	Sample prevalence (% [$CI_{95\%}$])		Fisher's exact test (*P* value [$CI_{95\%}$])
	hp (+)*	hp (-)	
Male	14.925 [8.314–25.34]	19.402 [11.705–30.419]	0.424 [0.306–0.542]
Female	20.895 [12.875–32.071]	44.776 [33.476–56.642]	
	PAN	BOD/ANT	
Male	16.417 [9.422–27.055]	17.91 [10.553–28.747]	0.098 [0.027–0.17]
Female	16.417 [9.422–27.055]	49.253 [37.652–60.936]	
	EN	ER	
Male	28.358 [18.97–40.093]	5.97 [2.345–14.369]	0.48 [0.36–0.6]
Female	58.208 [46.269–69.257]	7.462 [3.229–16.309]	
	MILD	MOD	
Male	28.358 [18.97–40.093]	5.97 [2.345–14.369]	0.48 [0.36–0.6]
Female	58.208 [46.269–69.257]	7.462 [3.229–16.309]	

* All abbreviations are as in FIGURE 1.

TABLE 3. Statistical measures of the degree of association between prevalences of *H. pylori*, RUT results and gastritis-associated variables shown in FIGURE 3.

	Sample prevalence (% [$CI_{95\%}$])		Fisher's exact test (*P* value [$CI_{95\%}$])
	U (+)*	U (-)	
hp (+)	10.447 [5.153–20.031]	25.373 [16.487–36.929]	0.131 [0.051–0.213]
hp (-)	31.343 [21.505–43.204]	32.835 [22.791–44.741]	
	PAN	BOD/ANT	
hp (+)	11.940 [6.176–21.832]	23.88 [15.268–35.325]	1.000 [-]
hp (-)	20.895 [12.875–32.071]	43.283 [32.104–55.191]	
	EN	ER	
hp (+)	32.835 [22.791–44.741]	2.985 [0.53–10.246]	0.472 [0.353–0.592]
hp (-)	53.731 [41.916–65.141]	10.447 [5.153–20.031]	
	LIGHT	MOD	
hp (+)	32.835 [22.791–44.741]	2.985 [0.53–10.246]	0.472 [0.353–0.592]
hp (-)	53.731 [41.916–65.141]	10.447 [5.153–20.031]	

*All abbreviations as in FIGURE 1. [-], when confidence interval is not necessary.

relevant statistical associations were found between the observed prevalences of histopathological results for *H. pylori* and RUT. It is worth noting that the prevalence of U(+) results was higher in patients whose histopathological result was hp(-) than in patients hp(+), which further reinforces the absence of association between the prevalences of these variables (Fisher's exact test, *P*=0.131, 95% CI of *P*: 0.051 to 0.213).

In FIGURE 3B, the prevalence of hp(-) is statistically lower in PAN than in BOD/ANT. However, this statistical difference was small in magnitude (~0.03%). In addition, no statistical relevant associations were found between the prevalences of histopathological results for *H. pylori* and gastritis topography (Fisher's exact test, *P*=1; see TABLE 3).

In FIGURE 3C, it is worth noting that the prevalence of EN is statistically higher than the prevalence of ER, regardless of whether the histopathological result was hp(+) or hp(-). However, no statistical relevant associations were found between the prevalences of gastritis category and histopathological results for *H. pylori* (Fisher's exact test, *P*=0.472, 95% CI of *P*: 0.353 to 0.592). Likewise, FIGURE 3D shows that the prevalence of MILD is statistically higher than the prevalence of MOD, regardless of whether the histopathological result was hp(+) or hp(-). However, no statistical relevant associations were found between the prevalences of gastritis level of activity and histopathological results for *H. pylory* (Fisher's exact test, *P*=0.472, 95% CI of *P*: 0.353 to 0.592; see TABLE 3).

DISCUSSION

The present cross-sectional study aimed to compare proportions of important risk factors to develop gastric cancer (e.g. gender, age, endoscopic findings, urease and *H. pylori*) within a sample of a high gastric cancer prevalence population (Belém, Pará, Brazil), e.g. analyze the chance that convenience sampling would result in an association as strong (or stronger) as that observed among variables prevalences. Surprinsingly, the results showed no statistically relevant associations among observed variables (see TABLES 1–3), allowing one hypothesizes that observed risk factors associated to gastric cancer might be lesser synergistic than is usually expected.

However, we must point out how many factors could have influenced the present results and, therefore, the strength of a null hypothesis to this alternative. For instance, the small size of this study (n=67) limit the strength of our alternative hypothesis and, therefore, of any inference beyond it, despite the evidence observed through data analysis. Another important factor to be considered in this context is variability in gastric biopsy acquisition. In the present work, the biopsy-based tests were performed based on fundal, antral and corpus biopsies, one histological sample obtained at each stomach site. Differently, the Sydney System recommends the acquisition of at least two biopsy specimens from antrum and corpus[13,14]. In contrast, even after the Sydney System establishment, some authors worked solely with antrum biopsies[15]. In addition, as gastritis with atrophy progresses, additional corpus biopsy is suggested as corpus' mucosa gradually becomes the unique site for *H. pylori* colonization in the stomach. Moreover, in the presence of peptic ulcer bleeding, acute gastritis, intestinal metaplasia, or gastric cancer, the gastric body greater curvature was described as the better site to detect *H. pylori* infections[16]. This variability indicates that there is no unique optimal sites to carry out a stomach biopsy yet, what certainly contribute to both false positive and negative results emerge in biopsy-based tests as RUT and histopathological exams for *H. pylori* detection.

Beyond the quality and site of the biopsy sample, factors inherent to biopsy-based tests used in the present work also could influence our results interpretation significantly. For instance, a true positive result in RUT requires approximately 10^5 *H. pylori* in the biopsy sample to produce the positive reaction[17]. Nonetheless, false-positive reactions also can occur, as bacteria other than *H.*

pylori possess urease activity and potentially colonize the gastric mucosa[18]. On the other hand, a negative result in RUT is not a reliable indicator of absence of *H. pylori* infection[19]. For instance, in patients treated with proton pump inhibitors and antibiotics for the eradication of *H. pylori*, the diagnosis needs to focus on an increased frequency of false-negative reactions of the RUT due to marked decreases in the *H. pylori* population[20]. In the present work, no information concerning treatment with proton pump inhibitors, antibiotics or other medicines was found in the medical records analyzed, since these records were made along diagnosis establishment and, therefore, prior prescription. In addition, the literature evidences that a significant number of false negative in histopathological results occur regardless the staining method used, variability in pathologists' microscopy skills, *H. pylori* distribution through the stomach in gastritis with atrophy and intestinal metaplasia, local production of antimicrobial factors and hypochlorhydria[21,22].

Although in the present work no statistical relevant associations were found between the prevalence of gastritis topography and patients' gender, differential protective immunity between genders may explain the higher prevalence of BOD/ANT in female than prevalence of BOD/ANT in male and prevalences of PAN in female and male, as observed in FIGURE 2 and TABLE 2[23]. On the other hand, in the literature the seroprevalence of *H. pylori* is equal in both genders, what is in agreement with the prevalences of hp(+) in both genders showed in the present work. However, while no statistical relevant associations were found between the prevalences of hp(+) and hp(-) and patients' gender in the present work, in the literature the male/female ratio ranges from 1.4 to 4 for gastric cancer[24]. Indeed, some authors support a small contribution of sex differences in the prevalence of infection to the male predominance of *H. pylori*-related outcomes, including gastric cancer[25]. Such discrepancies among seroprevalence of *H. pylori*, no association of histopathological results with patients' gender, and gender differences in gastric cancer prevalence, all support one hypothesizes that classical risk factors for gastric cancer might be lesser synergistic than is usually expected.

Other, and maybe yet unknown, host and environmental factors might be also important in the development of gastric cancer. Age dependent decrease in GMSH, a reduction in the number of mucous cells in the gastric mucosa of elderly, a decreasing prostaglandin concentration in the gastric mucosa of the elderly, a possible age-, gender- and *H. pylori*-related levels of ghrelin[26], all among a number of other variables, should be investigated to clear their potential synergistic role in gastric cancer onset.

CONCLUSION

In light of results of the present cross-sectional study, the authors hypothesize that observed risk factors associated to gastric cancer might be lesser synergistic than is usually expected. However, many arguments also exist in the literature supporting a null hypothesis to this alternative. Additional research should be carried out to clear this issue. As it is a multivariable problem, unsupervised machine learning approaches might be useful toward this aim.

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Authors' contribution

Miranda AC and Caldato C: patients care and endoscopic analysis. Miranda AC and Quaresma JAS: histopathological analysis. Miranda AC and Teixeira CEC: data analysis. Miranda AC, Said MN, Levy CS and Teixeira CEC: text writing.

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Miranda AC, Caldato C, Said MN, Levy CS, Teixeira CEC, Quaresma JAS. Gênero, idade, achados endoscópicos, urease e *Helicobacter pylori*: ausência de correlação dentro de uma amostra de população com alta prevalência de câncer gástrico na Amazônia. Arq Gastroenterol. 2019;56(3):264-9.

RESUMO – **Contexto** – É amplamente assumido que gênero, idade, gastrite e *Helicobacter pylori*, todos têm algum grau de correlação e, portanto, podem sinergicamente levar ao desenvolvimento de câncer gástrico. **Objetivo** – Neste estudo transversal, esperamos observar a correlação acima mencionada na análise de prontuários de 67 pacientes de ambos os sexos (sexo feminino, n=44), média de idade ± desvio padrão: 41±12 anos, todos de Belém (capital do Estado do Pará, Amazônia Brasileira), uma cidade historicamente conhecida como sendo uma das que apresenta maior prevalência de câncer gástrico no país. **Métodos** – Todos os pacientes foram submetidos à endoscopia digestiva alta para análise histopatológica da biópsia gástrica e teste rápido da urease. Todos os diagnósticos de gastrite foram registrados considerando sua topografia, categoria e grau de atividade inflamatória, sendo associada ou não associada à infecção por *H. pylori*. **Resultados** – Os resultados mostram que não foram encontradas associações estatisticamente relevantes entre as prevalências das variáveis observadas. **Conclusão** – Os autores levantam a hipótese de que os fatores de risco associados ao câncer gástrico podem ser menos sinérgicos do que o esperado.

DESCRITORES – Neoplasias gástricas. Endoscopia gastrointestinal. Caracteres sexuais. Fatores etários. Análise de variância. Urease. *Helicobacter pylori*.

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