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ORIGINAL ARTICLE

Assessment of Gastritis and Gastric Cancer Risk in the Chilean Population Using the OLGA System

Enrique Bellolio[1,2] · Ismael Riquelme[3] · Angela L. Riffo-Campos[1,4] · Carlos Rueda[5] · Catterina Ferreccio[6,7] · Miguel Villaseca[1,2] · Priscilla Brebi[1,8] · Sergio Muñoz[9] · Juan Carlos Araya[1,2]

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Abstract

Gastric cancer (GC) is the first cancer-related cause of death in Chile; however, no plan for GC early detection has been implemented in this country. The OLGA system characterizes gastritis from stages 0 to IV according to the risk of developing GC based on *H. pylori* infection, atrophy, metaplasia and GC. In this study, the performance of the OLGA system was evaluated in 485 Chilean patients receiving routine endoscopy to improve the detection of early GC or preneoplastic lesions. The results showed that OLGA scores, atrophy, metaplasia and GC increased significantly with age ($p < 0.001$). Conversely, *H. pylori* infection was higher in younger groups ($p < 0.05$). All gastric lesions were more frequent in men than women. The majority of patients with atrophy also had metaplasia (99%, $p < 0.0001$). Patients with *H. pylori* infection had more gastric atrophy and metaplasia than those without infection ($p < 0.05$). Of the 485 patients, 21 (4.3%) had GC, being 2.3 times more frequent among men than women and about 2/3 (14) were in OLGA stage ≥2. In addition, 19 (90%) GC patients had atrophy and 18 (85%) had metaplasia ($p < 0.001$). In conclusion, the OLGA system facilitated the evaluation of GC precursor lesions particularly in patients with an OLGA score > 2 between 45 and 56 years old, because this group showed atrophy and intestinal metaplasia more frequently. Therefore, biennial endoscopic surveillance of patients with an OLGA >2 can be an important health policy in Chile for diagnosing GC in its early stages and reducing mortality over the next two decades.

Keywords The OLGA system · Helicobacter pylori infection · Gastric atrophy · Metaplasia · Gastric cancer · Chilean population

Enrique Bellolio and Ismael Riquelme contributed equally to this work.

Enrique Bellolio and Ismael Riquelme are both first authors.

✉ Enrique Bellolio
enrique.bellolio@ufrontera.cl

✉ Ismael Riquelme
ismael.riquelme@uautonoma.cl

[1] Department of Pathological Anatomy, School of Medicine, Universidad de La Frontera, Avenida Alemania 0458, Postal Code, 4810296 Temuco, Chile

[2] Instituto de Patología Celular y Molecular, Lago Puyehue 01745, Postal Code, 4810469 Temuco, Chile

[3] Instituto de Ciencias Biomédicas, Facultad de Ciencias de la Salud, Universidad Autónoma de Chile, Avenida Alemania 01090, Postal Code, 4810101 Temuco, Chile

[4] Centro de Excelencia de Modelación y Computación Científica, Universidad de La Frontera, Calle Montevideo 740, Postal Code, 4811322 Temuco, Chile

[5] Gastroenterologist, Avenida Apoquindo 2880, Postal Code 7550000, Las Condes, Santiago, Chile

[6] School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile

[7] Advanced Center for Chronic Diseases (ACCDiS), FONDAP, Diagonal Paraguay 362- Santiago, Postal code, 8330024 Santiago, Chile

[8] Laboratory of Molecular Pathology, Department of Pathological Anatomy, School of Medicine, Center of Excellence in Translational Medicine - Scientific and Technological Bioresource Nucleus (CEMT-BIOREN), Universidad de La Frontera, Avenida Alemania 0458, Postal Code, 4810296 Temuco, Chile

[9] Department of Public Health, School of Medicine, Universidad de La Frontera, General Jose Miguel Carrera 228, Postal Code, 4781135 Temuco, Chile

Introduction

Gastric cancer (GC) is the fifth most common cancer and the third most lethal malignancy worldwide. Every year almost 1 million new GC cases are diagnosed and ~700,000 people die of this disease, which is ~10% of the world's cancer-related deaths [1]. The most affected populations are those from Eastern Europe, Asia and Central and South America [2]. In Chile, GC is also an important public health problem because it is the primary cause of cancer-related deaths in the entire population (19.2 deaths/100,000 people), affecting twice as many men as women [3–5]. The highest mortality rates in Chile are found in the regions of Maule, Bio-Bio and La Araucanía.

In general, this high mortality by GC is associated with the absence of significant symptoms in the early stages and a paucity of validated screening programs [6, 7]. In addition, the primary prevention of GC by eradication of its main causal agent - *Helicobacter pylori* - has not gained consensus [8]. Consequently, most GC cases are diagnosed at an advanced stage, with a poor prognosis due to the limited efficacy of conventional chemotherapy and surgery [9, 10]. Therefore, it is essential to find the early features for anticipating the development of GC, especially in those populations with high mortality rates such as the population in La Araucanía.

As *Helicobacter pylori*-related chronic gastritis is a crucial step in the development of intestinal-type GC [11–13], an efficient strategy might consist of monitoring the gastric mucosa through upper gastrointestinal endoscopy (UGE) and biopsy sampling in order to find those early lesions and then evaluating the risk of developing GC [14]. Despite UGE effectiveness, this methodology is generally limited by its invasiveness and cost; however, it remains the only available strategy for identifying those patients with a higher probability of developing this malignancy and who should receive a closer follow-up [14–16]. In this context, in developing countries a more accessible and low-cost methodology is needed.

An enhanced identification of high-risk patients has been observed using the operative link for gastritis assessment (OLGA) system [14, 17]. OLGA is a staging system to rank GC risk based on both the severity and location of gastric lesions using a topographical sampling of stomach tissue through anatomical coordinates (A1, A2, A3, C1 and C2) [18, 19], and includes information of the likely etiology of gastric inflammatory disease (e.g. *Helicobacter pylori* infection, autoimmune diseases, etc.), following the updated Sydney System recommendations [20]. Therefore, this classification arranges the histological phenotypes of gastritis along a scale of progressively increasing GC risk, from the lowest (OLGA stage 0) to the highest (OLGA stage IV) [21].

The value of OLGA score can be sustained by several articles suggesting its use as a valuable tool to assess the risk to develop of gastric cancer. For instance, a previous report have stated that those patients with metaplastic gastritis and presence of chronic atrophic gastritis (likely OLGA 4) have the highest risk (hazard ratio = 61.85) to develop gastric cancer [22]. Other authors have recently reported the usefulness of the OLGA system in cross-sectional studies in few some populations such as Korea [23, 24], Japan [25] and the Netherlands [26]; however, it has been stated that more studies in different epidemiological contexts are needed to validate the system [19]. In the present study, the presence of atrophy and various associated gastric diseases, including GC, using the OLGA system is reported. In addition, the applicability of this system in the Chilean population is discussed, in particular in a region with one of the highest mortality rates (27.3 per 100,000 habitants) in the country, particularly among men (35.7 per 100,000 habitants) as in La Araucanía [5].

Material Methods

Patients, Endoscopic Examination and Sampling

This is a cross-sectional descriptive study without follow-up. The participants were 485 symptomatic patients (306 women and 179 men) referred to endoscopy and with sample biopsy in Temuco, capital of La Araucanía region in Chile between 2011 and 2013. All patients duly signed an informed consent according to ethical requirements of WMA Declaration of Helsinki - Principles for medical research involving human subjects. Age range of subjects was 13 to 93 years and mean age was 54 years for women and 55 for men. All patients presented with 12 h fasting and were administered intravenous sedation with midazolam (0.05 mg per kg of weight) according to the Chilean Ministry of Health guidelines for this procedure. All endoscopies were performed by the same gastroenterologist (CR) using an Olympus Q230 endoscope (Olympus). Five gastric mucosa samples were obtained from each patient according to OLGA anatomical coordinates (A1, A2, A3, C1 and C2) [18]. Biopsy specimens were fixed in 10% buffered formalin.

Pathology Analysis

A single expert pathologist (EB) assessed reviewed all the biopsy specimens under microscope to assess morphology and pathological features. Hematoxylin and eosin staining were used as routine staining of samples, followed by periodic acid-Schiff (PAS) and Alcian blue stainings. Moreover, for analyzing chronic infection by *H. pylori*, methylene blue staining and Differential Quik (Diff-Quik) staining were used in all fragments. Each biopsy was classified according to OLGA staging (0, I, II, III, IV) and histopathology features: atrophy, metaplasia (complete and incomplete), *H. pylori* infection and GC) (Table 2). Then, each OLGA staging group of

biopsies was organized into four age groups (13–44, 45–56, 57–66 and 67–93 years old) (Table 3). Moreover, the severity of inflammation (combination of mononuclear and granulocytic cells), atrophy, and intestinal metaplasia were each graded as: "none", "mild", "moderate", and "severe", according to the updated Sydney System, and scored on a 0–3 scale, respectively (Table 4).

Statistical Analysis

The statistical analyses were performed using the STATA v14 (StataCorp) and R v3.2.2 software packages. The χ^2 test, contingency table, Fisher's exact probability and Mann–Whitney U test were used, as appropriate, for the data analysis. A p value <0.05 was considered significant. We performed a multivariate analysis to evaluate the predictive capacity of the OLGA for the various histological lesions adjusting for age and sex.

Results

Cohort Description

A total of 485 biopsy specimens were included for examination in this study, of which 306 (~63%) were from women and 179 (~37%) were from men. The age range of subjects was from 13 to 93 years old and the mean age for women was 54 years and 55 for men. The clinicopathological features of subjects are presented in Table 1.

OLGA Score According to Histopathological Alterations

Among these 485 participants, 228 (~47%) showed no type of alteration in the epithelium and 257 (~53%) subjects showed at least one mucosal lesion confirmed microscopically (Table 2). The prevalence of lesions (atrophy, metaplasia and cancer) was higher among men (37.4%) than women (30.1%). The mean age of subjects with lesion was 62.5 years and for those without lesions 51 years.

Interestingly, patients in OLGA stages I and II simultaneously showed the presence of gastric atrophy and metaplasia, and a low frequency of GC. This suggests that these stages are the starting point in the assessment of individuals with high risk to develop GC in order to perform a more comprehensive follow-up on them. This idea is reinforced in those few patients with the highest OLGA scores (III and IV), who concomitantly showed the most advanced lesions (atrophy, metaplasia and GC) despite the finding of metaplasia and GC not being the main purpose of OLGA system (Table 2).

Table 1 Cohort description and clinicopathological features

				Findings in gastric mucosa*									
Characteristics	**Frequency**		**Age mean**	**Age range**	**Non lesions**	*P-value*	***H. pylori***	*P-value*	**Atrophy**	*P-value*	**Metaplasia**	*P-value*	**GC**	*P-value*
Gender	n	%	years	years	n (%)		n (%)		n (%)		n (%)		n (%)	
Female	306	(63.1%)	54.53	13–93	215 (70.26%)	*0.0712*	90 (29.41%)	*0.3606*	91 (29.74%)	*0.1079*	91 (29.74%)	*0.1079*	9 (2.9%)	0.0635
Male	179	(36.9%)	55.28	14–93	111 (62.01%)		60 (33.52%)		66 (36.87%)		66 (36.87%)		12 (6.7%)	
Total	**485**	**100%**	**54.9**	**13–93**	**326/485**		**150/485**		**157/485**		**157/485**		**21/485**	

*This section of Table 1 shows absolute frequency by sex; however, % of individuals are adjusted by sex (% within all females and % within all males)

**Chi-Square Test

Table 2 Histopathological alterations according to OLGA stages

	OLGA Stages					
Lesions	**0**	**I**	**II**	**III**	**IV**	**Total per lesions**
Non lesion	228	0	0	0	0	**228 (100%)**
H. pylori	97 (64.7%)	33 (22.0%)	19 (12.7%)	1 (0.6%)	0	**150 (100%)**
Atrophy	0	105 (66.9%)	43 (27.4%)	5 (3.2%)	4 (2.5%)	**157 (100%)**
Metaplasia	1 (0.6%)	105 (66.9%)	42 (26.8%)	5 (3.2%)	4 (2.5%)	**157 (100%)**
Gastric cancer	2 (9.5%)	5 (23.8%)	6 (28.7%)	4 (19.0%)	4 (19.0%)	**21 (100%)**
Total	**328**	**248**	**110**	**15**	**12**	**485 (100%)**

Then, each OLGA staging group was sub-classified according to age into four ranges (13–44, 45–56, 57–66 and 67–93 years old). To establish each age interval, a similar number of patients and a homogeneous gender distribution were considered within each group (Table 3). Most individuals were in stage 0 and total frequencies were decreasing until stages III and IV. Interestingly, as the subjects' age increased, the frequency of individuals with higher OLGA scores also increased, which demonstrates a significant correlation between these two variables ($p < 0.05$).

When both sexes were compared, men evidenced a non-significant trend of risk to develop more GC than women (OR: 2.37; 95% CI, 0.98–5.74; $p = 0.055$). This risk of developing GC became significant in men from 67 years old (OR: 5.5; 95% CI: 1.98–15.29; $p < 0.01$).

Inflammation Assessment

Inflammation assessment showed significant differences between the high frequencies of mild, moderate and severe inflammation mainly in the gastric antrum (A1, A2 and A3) compared to those frequencies found in the gastric corpus (C1 and C2) ($p < 0.05$, Table 4). Interestingly, A1 and A2 showed similar frequencies to A3 ($p < 0.05$). As the OLGA system can easily assess Correa's multi-step events, these findings may be related to the anatomical location of a potential intestinal-type GC, which is mainly located in the antrum, rather than to diffuse-type GC, which has no early stratified mucosal lesions and is primarily located closer to the esophagus (corpus or fundus).

Helicobacter Pylori Infection

A significantly higher frequency of *H. pylori* infection was observed in the two younger age groups, most importantly in patients between 45 and 56 years old ($p < 0.05$) (Fig. 1a). More interestingly, of the 21 patients with GC, only 3 (14.3%) individuals also had the *H. pylori* infection and their ages were ≤ 56 years old.

From the total 485 patients, 150 (30.3%) had the *H. pylori* infection, of which 90 (60% of infected subjects) were men and 60 (40% of infected subjects) were women. Therefore, the *H. pylori* infection has been shown to be more strongly associated with the male gender ($p < 0.001$) (Table 1). In addition, complementary association analyses showed that a third of patients with the *H. pylori* infection already had gastric atrophy (53 cases: 29 women and 24 men), demonstrating a strong association between these two abnormal events ($p < 0.01$). The same phenomenon occurs when assessing the association between the *H. pylori* infection and metaplasia ($p < 0.01$).

In our cohort, we also found that pathological alterations such as atrophy (OR: 1.24; 95% CI: 0.82–1.86; $p > 0.05$), metaplasia (OR: 1.27; 95% CI: 0.84–1.9; $p > 0.05$) and GC (OR: 0.36; 95% CI: 0.1–1.24; $p > 0.05$) seemed not to be directly attributable to *H. pylori* infection; however, these results can be explained because it is known that these alterations are consequence of a long-term *H. pylori* infection which were not defined by our experimental design based on a cross-sectional descriptive study without follow-up of individuals.

Table 3 Stage of atrophy according to age intervals of patients

	OLGA Stages					
Age ranges	**0**	**I**	**II**	**III**	**IV**	**Total per age**
13–44	110 (90.9%)	8 (6.6%)	3 (2.5%)	0	0	121 (100%)
45–56	87 (69.6%)	27 (21.6%)	9 (7.2%)	2 (1.6%)	0	125 (100%)
57–66	75 (60.0%)	35 (28.0%)	13 (10.4%)	1 (0.8%)	1 (0.8%)	125 (100%)
67–83	56 (49.1%)	35 (30.7%)	18 (15.8%)	2 (1.8%)	3 (2.6%)	114 (100%)
Total	**328 (67.6%)**	**105 (21.6%)**	**43 (8.9%)**	**5 (1%)**	**4 (0.9%)**	**485 (100%)**

Table 4 Inflammation grade according to anatomical location

	Anatomical Location				
	A1	A2	A3	C1	C2
Grade of Inflammation					
Mild	95 (63.8%)	81 (59.1%)	59 (59.6%)	44 (78.6%)	26 (74.3%)
Moderate	46 (30.9%)	46 (33.6%)	32 (32.3%)	7 (12.5%)	4 (11.4%)
Severe	8 (5.3%)	10 (7.3%)	8 (8.1%)	5 (8.9%)	5 (14.3%)
Total with lesions	149 (100%)	137 (100%)	99 (100%)	56 (100%)	35 (100%)
Total without lesions	336	348	386	429	450

Atrophy and Metaplasia

Among the 157 (32.3%) patients with atrophy, 91 (58.0%) were women (29.7% of all women) and 66 (42.0%) patients were men (36.9% of all men). Analysis adjusted for gender demonstrated that men had 7.1% more atrophic gastritis than women ($p < 0.05$). On the other hand, 157 patients showed metaplasia (32.8% of all cases with abnormal diagnosis) and almost all of these subjects also had atrophy ($p < 0.0001$), with only one exception that showed atrophy without metaplasia. Therefore, the same above-described associations regarding age and gender for atrophic gastritis also apply to metaplasia.

Interestingly, the atrophy frequency increased significantly as the patients' age increased ($p < 0.01$, Fig. 1b). Particularly, a higher frequency of atrophic gastritis was observed in men than women between 67 and 93 years (30 men vs. 28 women). When these values were corrected for gender but not for the total of analyzed cases, men were shown to develop significantly more atrophy than women ($p < 0.01$). In the metaplasia cases, the frequencies increased slightly with the increasing

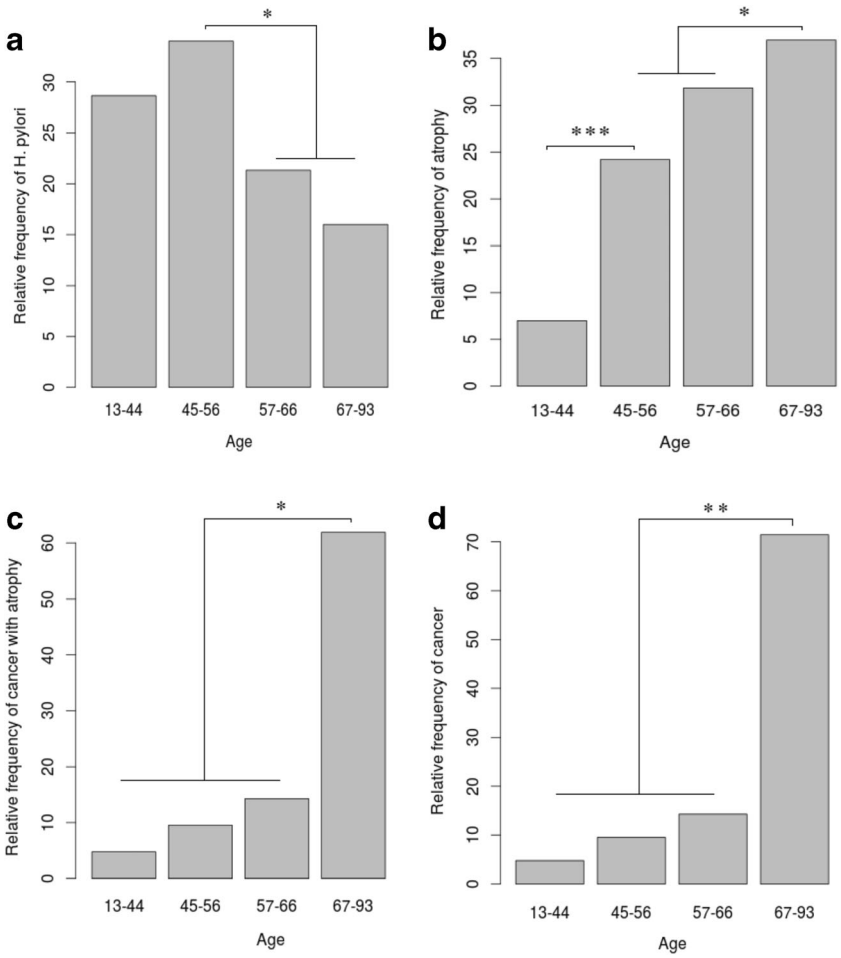

Fig. 1 Relative frequency of gastric lesions according to patients' age intervals. **a** Frequency of *H. pylori* infection according age range. **b** Frequency of atrophy according to age range. **c** Frequency of GC along with atrophy according to age range and **d** Frequency of GC according to age range

age of patients, but this increase was significant only for the oldest age group ($p < 0.01$, Fig. 1c).

Gastric Cancer

Among the 485 patients, 21 (4.3%) presented advanced GC that were classified according to Lauren's classification as: 19 intestinal-type adenocarcinomas (4 cases located in antrum, 1 case located in subcardial area and 14 cases whose location information was not available); and 2 diffuse-type adenocarcinomas (whose location information was not available). Of these 21 GC patients, 9 were women (2.9% of all women) and 12 were men (6.7% of all men). Therefore, the prevalence rate ratio for all age groups showed that GC was 2.3 times more frequent in men than women. In the older age group (67–93 years), the prevalence rate ratio for GC is about 4.4 times more frequent among men than women. The cancer frequencies increased slightly as the patients' age increased; however, as occurred in metaplasia, the difference was significant only for those patients in the oldest age group ($p < 0.01$, Fig. 1c and d). The difference between men and women is because in the older age group the prevalence ratio is higher.

Of all the 21 GC patients, 19 (90.5%) had concomitant gastric atrophy ($p < 0.001$) and 18 (85.7%) had also metaplasia ($p < 0.001$), compared to 29.9% and 30% of patients without GC. This confirmed the expected correlation among these three histological events. Men presented more GC and atrophy, which were directly associated with age.

Discussion

In the present study, the correlation between atrophy and other gastric abnormalities, including GC, was examined using the OLGA system in subjects belonging to a GC high-risk population such as the one in La Araucanía. The results showed that women were subjected to significantly more endoscopic procedures than men; however, in summary men turned out to be more affected by gastric abnormalities.

More interestingly, the *H. pylori* infection was more frequent in ≤56-year-old patients (45–56 years range) and was related to a low OLGA score (0, I or II). The presence of the *H. pylori* infection decreased slightly through the older groups, which showed higher OLGA scores. A previous study conducted by Nam et al. on the Korean population showed that people 40 years old or older were the most affected by the *H. pylori* infection. Nam et al.'s study also showed that high-risk OLGA stages were not found in participants younger than 30 years old, conversely to the *H. pylori* status. Therefore, Nam et al. suggest that the most appropriate age for *H. pylori* eradication may be before 30 years, which is before the high-risk gastritis stages start to increase [24]. Moreover, eradication of *H. pylori* for people at a low-risk stage of OLGA can prevent most gastric cancers, and surveillance endoscopy may not be necessary at all [24]. The present study shows that the *H. pylori* infection is more prevalent in patients under 56 years; therefore, a Chilean screening program for the *H. pylori* infection should be implemented for the detection, early diagnosis and treatment in patients under 56 years. The implementation of this non-invasive or less-invasive system for detecting the *H. pylori* infection could include techniques such as the ^{13}C-urea breath test, detection of anti-CagA/VacA antibodies or molecular tests [27]. This system would help to implement a timely treatment for this infection in symptomatic patients at early ages and thus avoid the harmful carcinogenic sequence in the stomach (atrophy, metaplasia) that ultimately ends in an intestinal-type GC. In addition, it is expected that this *H. pylori* treatment in patients under 40 years old could reduce the need for gastric cancer surveillance and its associated costs.

Conversely, as the presence of atrophy and metaplasia is more frequent in patients older than 56 years, this Chilean screening program should focus on performing upper digestive endoscopies in patients older than 50 years in order to detect early precursor lesions such as atrophy and metaplasia and avoid the development of GC.

On the other hand, there is a significant association between atrophic gastritis and gender, with men being the most affected group. This idea is consistent with previous reports stating that, in Chile, men suffer more atrophic gastritis and gastric cancer than women [3, 4, 28], but this seems to differ from the findings observed in a population of Japanese origin whose prevalence of *H. pylori* infection and chronic atrophic gastritis were similar between both sexes [29]. As expected, the cancer frequencies increased slightly as the patients' age increased and, as occurred in atrophy, the difference was again significant only for those patients in the older age range. Surprisingly, the three patients with GC within the third age range (57–66 years old) were women.

Additionally, we have found that the highest atrophy frequency was present in antral mucosa (A1, A2 and A3), which partly explains Correa's theory regarding the initial damage being of an antral type and extending to the corpus mucosa, then becoming pangastric atrophy or multifocal gastric atrophy with or without association with intestinal metaplasia [13, 30].

The majority of patients with OLGA stages I and II simultaneously showed the presence of gastric atrophy and intestinal metaplasia despite the low frequency of GC in our cohort. Therefore, OLGA stage II could be suggested as a starting point for a periodical monitoring of individuals at risk of developing GC in our population. Interestingly, in our cohort, atrophy and intestinal metaplasia coexisted in most samples and it was not possible to anticipate or distinguish atrophy versus metaplasia.

Previous studies have stated the relationship between the severity of preneoplastic lesions (atrophic gastritis or metaplasia) and the risk of developing GC; however, despite we suspect about a similar correlation in our cohort, we could not confirm it due to our experimental design is based on a cross-sectional descriptive study without follow-up. Some authors have showed an association between the severity of atrophic gastritis and the risk of GC, for example, Tatsuta et al. [31] who performed a follow-up study of 690 patients with benign gastric diseases and assessed the extent of fundal atrophic gastritis using the endoscopic Congo red test. A positive linear relationship between the risk of GC and the extent of fundal atrophic gastritis was observed. Ohata et al. [22] conducted a longitudinal cohort study (7.7 years follow up) and showed that the hazard ratio of GC was highest in patients with the most extensive atrophic gastritis assessed by serum pepsinogen. In fact, they stated that those patients with metaplastic gastritis, with negative values of anti-*H. pylori* antibodies and presence of chronic atrophic gastritis (likely OLGA 4) have a hazard ratio of 61.85 to develop gastric cancer. Sipponen et al. [32] showed risk (odds) of GC in different phenotypes of atrophic gastritis as compared to the cancer risk in subjects with normal and healthy stomach mucosa and the odds of which were 10–90 in patients with stage IV. Therefore, undoubtedly those patients with OLGA high-risk stages (III or IV) should be offered endoscopic surveillance to carefully examine the potential development of GC. Otherwise, a multivariate analysis did not show any significant association between the OLGA score and the worst histological lesions. Increasing the sample size and a longer follow-up would likely enhance this issue.

On the other hand, when individuals were grouped according to age, it was observed that as the age of the subjects increased, the frequency of individuals with higher OLGA scores also increased, demonstrating a significant correlation between these two variables. This correlates with previous studies that found similar results [24, 33, 34].

As updated Chilean statistics state that men have ~ two-fold greater frequency and mortality by GC than women [5], this study may help to posit the need to implement new public health strategies based on OLGA system screening in men between 45 and 56 (mean = 50) years old in order to enhance the follow-up of individuals and subsequently decrease the deaths by GC. For instance, if the initial OLGA score is >2, the follow-up should be more meticulous and frequent along the years than patients with lower scores. In fact, in 2014 the Chilean Consensus on Gastric Preneoplastic Lesions proposed that these kinds of patients be re-evaluated within 1 or 3 years as a follow-up policy. In conclusion, the OLGA system is a very useful tool for predicting the behavior of GC precursor lesions, particularly in a population with a high frequency/mortality by GC as the Chilean population. Our results suggest that higher OLGA stages are found in patients with atrophic gastritis or metaplasia (lesions that trigger GC) and that the high risk of GC can be recognized and treated on time. It may lead to the early diagnosis and secondary prevention of gastric cancers. In addition, biennial gastric cancer surveillance by endoscopy for those patients with an OLGA score > 2, as secondary prevention, can be an important policy in Chilean health system to reduce GC mortality. This policy has already been introduced nationwide in countries such as Korea for individuals aged 40 years and older and can be implemented in Chile.

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Compliance with Ethical Standards

Informed consent was obtained from all individual participants included in the study according to ethical requirements of WMA Declaration of Helsinki - Principles for medical research involving human subjects. We declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. The funders (see Acknowledgements) had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of Interest The authors have no conflicts of interest to declare.

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