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ORIGINAL ARTICLE

Observational Study

Prevalence of *Helicobacter pylori* infection among patients with esophageal carcinoma

Miriam López-Gómez, Maria Morales, Rebeca Fuerte, Marta Muñoz, Pedro-David Delgado-López, Jorge Francisco Gómez-Cerezo, Enrique Casado

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Abstract

BACKGROUND

Helicobacter pylori (*H. pylori*) is a widespread microorganism related to gastric adenocarcinoma (AC). In contrast, it has been reported that an inverse association exists between *H. pylori* infection and esophageal carcinoma. The mechanisms underlying this supposedly protective effect remain controversial.

AIM

To determine the prevalence of *H. pylori* infection in esophageal carcinoma

patients, we performed a retrospective observational study of esophageal tumors diagnosed in our hospital.

METHODS
We retrospectively reviewed the prevalence of *H. pylori* infection in a cohort of patients diagnosed with esophageal carcinoma. Concomitant or previous proton pump inhibitor (PPI) usage was also recorded.

RESULTS
A total of 89 patients with esophageal carcinoma (69 males, 77.5%), with a mean age of 66 years (range, 26-93 years) were included. AC was the most frequent pathological variant (n = 47, 52.8%), followed by squamous cell carcinoma (n = 37, 41.6%). Fourteen ACs (29.8%) originated in the gastroesophageal junction and 33 (70.2%) in the esophageal body. Overall, 54 patients (60.7%) presented at stages III and IV. Previous *H. pylori* infection occurred only in 4 patients (4.5%), 3 with AC (6.3% of all ACs) and 1 with squamous cell carcinoma (2.7% of all squamous cell tumors). All patients with previous *H. pylori* infection had stage III-IV. Only one patient had received prior *H. pylori* eradication therapy, whereas 86 (96.6%) had received previous or concomitant PPI treatment.

CONCLUSION
In our cohort of patients, and after histologic evaluation of paraffin-embedded primary tumors, we found a very low prevalence of previous *H. pylori* infection. We also reviewed the medical history of the patients, concluding that the majority had received or were on PPI treatment. The minimal prevalence of *H. pylori* infection found in this cohort of patients with esophageal carcinoma suggests a protective role.

Key Words: *Helicobacter pylori*; Eradication; Esophageal tumor; Dysbiosis; Proton pump inhibitors; Carcinogenesis; Microbiota; Incidence

Core Tip: *Helicobacter pylori* (*H. pylori*) is involved in gastric carcinogenesis and its eradication has become widely accepted. However, recent studies suggest that it might have a role in maintaining homeostasis in the gastroesophageal junction cells and may have a protective role in esophageal carcinogenesis. The absence of this microorganism might contribute to dysbiosis and alterations in the esophageal microenvironment which might finally be involved in the onset of esophageal tumor. We are very much concerned that the prevalence of esophageal cancer increases after the universalization of *H. pylori* eradication.

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INTRODUCTION

Esophageal cancer constitutes a relevant health problem, being the sixth cause of death attributable to cancer worldwide [1]. There are two major histological subtypes: Esophageal squamous cell carcinoma (SCC) and adenocarcinoma (AC). The incidence of AC has increased in the recent decades, currently accounting for almost half of all esophageal neoplasms [2]. Well-established risk factors for AC include Barrett's esophagus (BE), gastroesophageal reflux (GER), male sex, central obesity, older age, and tobacco smoking[3]. Interestingly, *Helicobacter pylori* (*H. pylori*) eradication with antibiotics and acid suppression therapies seem to be protective in gastric cancer[4]. *H. pylori* is a helical-shaped Gram-negative (GN) bacterium that generally colonizes the stomach early in life[5].

The estimated global prevalence of *H. pylori* infection has decreased from 58.2% (95%CI: 50.7-65.8) in the 1980-1990 decade to 43.1% (40.3%-45.9%) in the 2011-2022 period[6]. In Spain, studies report a population prevalence around 55% [7].

The prevalence of *H. pylori* infection in gastric cancer patients seems to vary among regions, with the highest and lowest figures in America and Africa, respectively (18.1%, 95%CI: 16.5-19.6 *vs* 9.5%, 95%CI: 5.9-13.1)[8].

However, a higher prevalence has been reported in other gastrointestinal malignancies. In a Finnish study, prevalence ranged from 100% for gallbladder cancer to 94% for ampulla of Vater cancer. Similarly, the prevalence of *H. pylori* infection in hepatocellular carcinoma has been reported to be up to 94%[9]. *H. pylori* has also been found in 86% patients with advanced colon neoplasia[10]. Proton pump inhibitors (PPIs) are classically prescribed for the treatment of acid-related gastrointestinal disorders and are part of the multidrug treatment for *H. pylori* eradication[11]. However, long-term administration of PPI can change the microbial composition in the esophagus[12] which might contribute to the development of BE and esophageal cancer. The role of *H. pylori* in the origin of gastric ACs has been thoroughly studied and its eradication has become one of the greatest challenges worldwide[13].

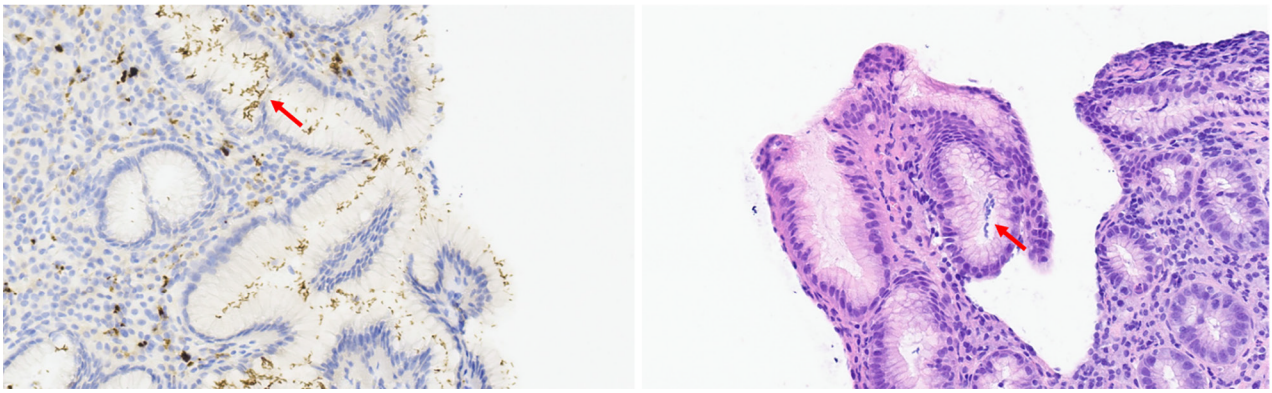

Figure 1 Red arrows show *Helicobacter pylori* in the lumen of gastric mucosa.

Interestingly, the presence of *H. pylori* infection has been associated with a reduced risk of the development of esophagus ACs[14]. The underlying mechanisms responsible for this protective effect remain unclear. Several hypotheses have been suggested: *H. pylori* induced atrophy and loss of the acid parietal cells in the antrum[15]; secondary alteration of esophageal microbiota[16]; induction of apoptosis of AC cells progressing from BE *via the* Fas apoptotic pathway[17], and ghrelin synthesis reduction, with a secondary impact on central obesity and GER[18].

Considering that *H. pylori* eradication has become a widely accepted healthcare policy in Spain, concerns about a plausible increase in esophageal cancer have grown. In this study we reviewed the prevalence of pre-existent *H. pylori* infection among patients with esophageal carcinoma and recorded which of them were on previous PPI treatment, either as part of the eradication therapy or for other reasons.

MATERIALS AND METHODS

Study design

We performed a retrospective observational study that included all patients with a previous diagnosis of esophageal or gastroesophageal junction (GEJ) cancer between February 2008 and December 2023 and were managed at our center. Local Institutional Review Board approval was obtained on June 1, 2023. All patients or relatives were informed and accepted participation by signing a written informed consent form. Patients' data were anonymized according to national regulations (RD 1720/2007, Organic Law 15/1999 on Personal Data Protection).

Patient selection

All patients over 18 years of age with a diagnosis of esophageal or GEJ cancer were included. Patients with gastric or other gastrointestinal neoplasms were excluded from the study. The incidence of *H. pylori* in gastric cancer patients diagnosed throughout the same years (2008 and 2022) were also included in the analysis.

In situ tumors or premalignant lesions were also excluded. All patients included agreed to participate in the study.

Tumor subtype and H. pylori infection identification

All tumors (esophageal or GEJ invasive tumors) were histologically confirmed by trained pathologists of the center. Paraffin-embedded primary tumor specimens and metastatic tumor specimens containing at least 70% of tumoral cells were selected for each patient. Specimens were reviewed and classified into three subtypes: AC, SCC, and others. The presence or absence of *H. pylori* was also confirmed by histologic examination. Definitive diagnosis was made by microscopic visualization of *H. pylori* on hematoxylin and eosin (H&E)-stained slides. Positive cases of *H. pylori* included patients with obvious *H. pylori* gastritis with characteristic inflammation and heavy bacterial load, and those with subtle *H. pylori* gastritis with less inflammation and fewer bacteria. Two examples of *H. pylori* identification are shown in Figure 1 (gastric cancer) and Figure 2A (GEJ cancer). Figure 2B and C show H&E staining of GEJ and esophageal tumors.

Variables registered, endpoint and statistical analysis

In addition to the presence or absence of *H. pylori* in biopsy specimens, the following variables were recorded: Age, sex, tumor stage at diagnosis, and previous treatment with anti-acid drugs (PPIs or others, as part of *H. pylori* eradication therapy or as independent treatment). The endpoint of the study was the identification of *H. pylori* infection in patients diagnosed with esophageal cancer. Results were expressed as mean ± SD for numerical variables, and as ratios and proportions for categorical variables, both with 95%CI.

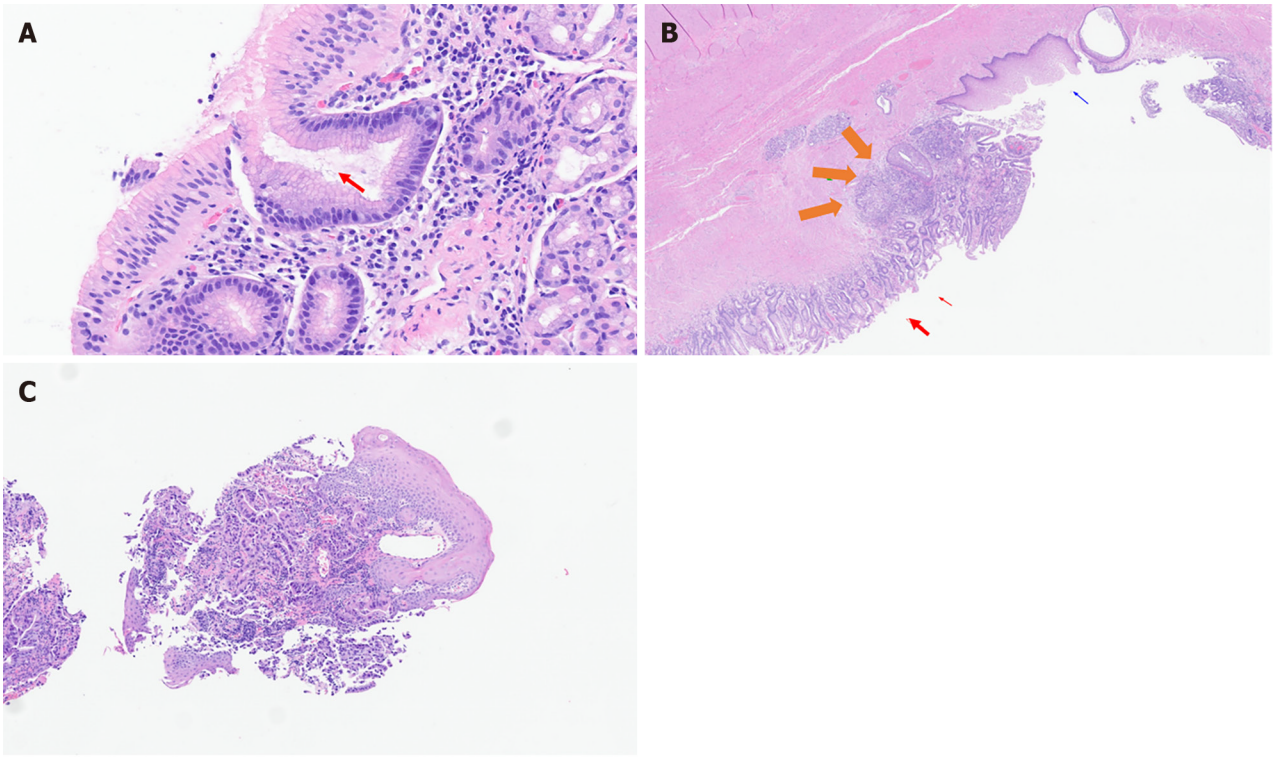

Figure 2 Gastroesophageal junction and esophageal tumors. A: Red arrow shows *Helicobacter pylori* in the lumen of an esophageal gland; B: Gastroesophageal junction (GEJ) tumor. Blue arrow shows squamous cells in normal esophageal tumors. Red arrows show Barrett's esophagus. Orange arrows show GEJ adenocarcinoma; C: Esophageal adenocarcinoma.

RESULTS

Demographic and clinical data

A total of 89 patients (77.5% males, mean age 66 years) were included in our study. Demographic and clinical data are shown in Table 1.

Tumor statistics

In this cohort, AC was the most frequent histological subtype (52.8%) followed by SCC (41.6%). Neuroendocrine tumors were infrequent (5.6%). As expected, most tumors were stage III-IV at the time of diagnosis (60.7%). *H. pylori* infection was confirmed in only 4 patients (4.5%), 3 with AC and 1 with SCC. Survival among *H. pylori* positive patients did not exceed 9 months after diagnosis (Figure 3). Although only one patient had undergone previous *H. pylori* eradication therapy, 96.6% of patients had received prior PPI treatment and 35.9% (n = 32) had received both PPIs and other antiacid treatment (such as anti-H_2 or sucralfate). The median time from initiation of PPIs to the diagnosis of esophageal cancer was 15 months, ranging from 3 to 60 months (Figure 4). Total gastric cancer diagnoses were 431, with a rate in men/women of 269/162 (62.41% *vs* 37.58%). The mean age was 66 years. *H. pylori* prevalence among them was 66%.

DISCUSSION

H. pylori infection and esophageal cancer are conditions with a high geographical variability and prevalence. The purpose of this study was to analyze the prevalence of *H. pylori* in esophageal tumors in a sample of patients from a tertiary hospital in Madrid, Spain. In this cohort, less than 5% of patients with esophageal cancer tested positive for *H. pylori*, which is approximately 10 times less than the general population. Interestingly, most of them had received previous antiacid treatment, either with PPIs or with anti-H2 drugs.

The burden due to the diagnosis of esophageal cancer is expected to rise dramatically across high-income countries, with increasing incidence rates predicted for the next decades, according to some statistical models[19].

Previous epidemiologic studies provide inconclusive data on a positive, inverse or neutral association between *H. pylori* infection and esophageal carcinoma. Although meta-analyses of observational studies favor an inverse association, these may be biased by confounders present in older studies (Table 2). Our findings are in line with this supposedly protective role of *H. pylori* infection in the genesis of esophageal carcinoma.

To date, four meta-analyses have shown an inverse association between *H. pylori* infection and esophageal cancer. Islami and Kamangar[20] reviewed 19 studies (Table 2) and found an inverse association between cytotoxin-associated gene A (CagA)-positive strains of *H. pylori* and the risk of esophageal carcinoma [odds ratio (OR) 0.41, 95%CI: 0.28-0.62].

Table 1 Baseline characteristics of all patients, *n* (%)

Number of patients	*n* = 89
Age (median, yr)	66 (26-93)
Sex	
Male	69 (77.52)
Female	20 (22.47)
Histology	
Adenocarcinoma	47 (52.80)
Squamous cell carcinoma	37 (41.57)
Others	4 (5.5)
Tumor location	
Gastroesophageal junction	33 (70.21)
Esophageal	14 (29.78)
Stage	
Stage I-II	25 (28.08)
Stage III-IV	54 (60.67)
Presence of *Helicobacter pylori*	4 (4.5)
Adenocarcinoma	3 (6.3)
Squamous cell carcinoma	1 (2.7)
Previous PPI treatments	86 (96.82)

PPI: Proton pump inhibitor.

Table 2 Studies regarding *Helicobacter pylori* infection and esophageal carcinoma

Paper characteristics				Sample characteristics			
Ref.	Country	Year	Design	Age (mean, yr)	*Helicobacter pylori* prevalence	Tumor	Location
Holleczek *et al* [23]	Germany	2020	Cohort	62.2	47.80%	EA	Gastric cardia; esophagus esophago-gastric junction
Wu *et al*[27]	Taiwan	2009	Case-control	58.3	35.30%	ESCC	Upper, middle or lower third of the esophagus
Khoshbaten *et al* [28]	Iran	2011	Case-control	63.9 cases; 61.3 controls	41.2% ± 36.95% cases; 56.2% ± 29.5% controls	ESCC	Esophagus
Hu *et al*[29]	Taiwan	2009	Case-control	50-70	37% cases; 53% controls	ESCC	Upper, middle or lower third esophagus
Cook *et al*[30]	Finland	2010	Case-control	57.7 cases; 58.1 controls	80.28% cases; 78.16% controls	ESCC	Upper, middle, and lower third of the esophagus
Murphy *et al*[18]	Finland	2012	Case-control	57.9 cases; 57.9 controls	78.04% cases; 76.82% controls	ESCC	Esophagus

EA: Esophageal adenocarcinoma; ESCC: Esophageal squamous cell carcinoma.

A similar conclusion was stated by Zhuo *et al*[21], in a study that included 195 articles, and found a risk of developing esophageal AC among *H. pylori* infected patients of 0.58 (95%CI: 0.48-0.70) as compared with controls. Xie *et al*[22], also confirmed this inverse association in the general population (0.59, 95%CI: 0.51-0.68, and an OR of 0.56, 95%CI: 0.45-0.70 in Cag A+ strains). However, results from these meta-analyses were based on retrospective observational studies. Only one population-based prospective study[23] conducted in Germany, which included 9949 patients followed for a mean period of 13.8 years, found a 0.65-fold increase risk of developing esophageal carcinoma among *H. pylori* infected individuals.

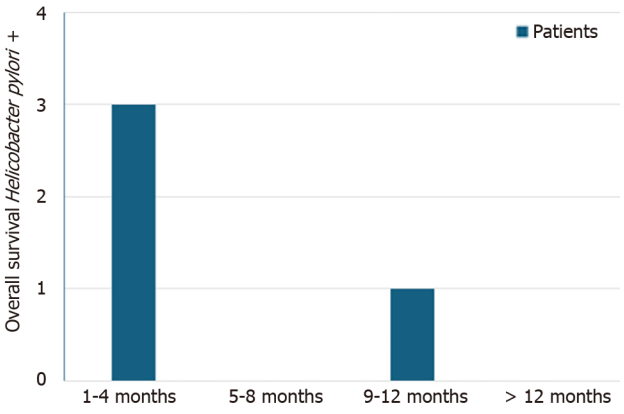

Figure 3 Survival among *Helicobacter pylori* positive patients.

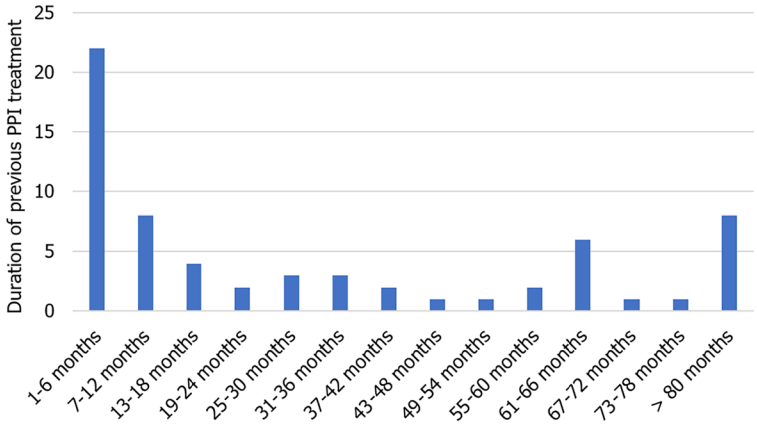

Figure 4 Duration of proton pump inhibitor treatment before cancer development. PPI: Proton pump inhibitor.

These findings support the need for further research on the inner mechanisms behind this association. Several plausible pathways have been suggested. First, *H. pylori* infection-related gastritis induces atrophy and loss of parietal cells in the stomach, resulting in a reduced reflux which decreases related-esophagitis and BE; second, *H. pylori* infection might induce apoptosis in Barrett's cells through the Fas-Caspase cascade; third, *H. pylori* could promote inflammatory responses by activating nuclear factor kappa B, that induces the production of certain cytokines and tumor necrosis factor-alpha, directly damaging the epithelial DNA by dysregulating DNA transcription factors such as the caudal type homeobox 2 (Cdx2); fourth, *H. pylori* infected patients have a significantly lower number of ghrelin producing cells, which has been shown to be involved in cancer development and metastasis[24].

Additionally, an interesting and promising relation between *H. pylori* infection and the esophageal microbiome has been suggested. In the normal esophageal mucosa, *Streptococcus spp.*, together with six other major phyla (*Firmicutes*, *Bacteroides*, *Actinobacteria*, *Proteobacteria*, *Fusobacteria* and *TM7*) are the most commonly found microorganisms belonging to the local microbiota. Type I microbiota, which is mainly composed of gram-positive (GP) bacteria, is typically found in the normal esophagus mucosa. In contrast, type II microbiota, enriched in GN bacteria, is associated with an abnormal esophagus. *H. pylori* infection might play a role in the shift from GP to GN-enriched environment. Previous studies have reported that *H. pylori* seems to influence gastric microbiome diversity and composition and affects species prevalence and phylogenetic diversity. In fact, esophageal tumors colonized by *H. pylori* CagA positive strains were inversely associated with the risk of developing esophageal AC. These findings suggest that the absence of *H. pylori* in the gastroesophageal mucosa might contribute to an unbalanced esophageal microbial composition that may promote carcinogenesis[25].

Similarly, PPI treatment has been suggested to alter the esophageal microbiota, by increasing species like *Firmicutes* and decreasing *Bacterioides* and *Proteobacteria*. A recent study has suggested that the long-term use of PPIs is associated with an increased risk of esophageal cancer[26], likely attributable to the colonization of non-gastric microorganisms capable of producing nitrosamines, which are known to promote both esophageal AC and SCC. In our cohort, almost 95% of patients were under PPI treatment, in line with this hypothesis. PPIs-induced reduction of esophageal gastric acid reflux might avoid the death of acid sensitive bacteria involved in the maintenance of type I microbiota. This hypothesis might be in conflict with recommending PPIs in non-dysplastic BE, aimed to decrease the risk of progression to high grade dysplasia and AC. Considering the widespread use of PPIs, we believe our findings maintain a reasonable doubt on the possible deleterious effect of this medication in the development of esophageal cancer.

This study has some limitations. Most importantly, given the observational and retrospective nature of the study, a causal relation between the lack of *H. pylori* infection and esophageal cancer cannot be established. Second, as we did not include a non-PPI treatment control group, we cannot conclude on the relation between PPI therapy and esophageal carcinogenesis. Finally, although the results of a single center study may not be extrapolated to other populations, it highlights the importance of further research on the role of *H. pylori,* and other microorganisms belonging to the local microbiota, in esophageal carcinogenesis.

CONCLUSION

The very low prevalence of *H. pylori* infection among esophageal cancer patients found in our study is consistent with previous reports suggesting that the presence of *H. pylori* might have a protective role in esophageal carcinogenesis. Several mechanisms have been proposed for this inverse association, in which esophageal mucosa dysbiosis seems to play a primary role. Future research should determine to what extent *H. pylori* infection interacts with the esophageal microbiota, establish whether this interaction is involved in the protective role of *H. pylori*, and whether PPI treatment contributes to the alteration of esophageal microbiome and eventually promotes esophageal cancer.

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FOOTNOTES

Author contributions: López-Gómez M and Morales M wrote the manuscript; Morales M and Fuerte R curated the clinical data and performed the biostatistical analyses; Muñoz M selected the tumor tissue to be analyzed; Delgado-López PD drafted/edited the manuscript and reviewed the English version; Gómez-Cerezo JF and Casado E helped with clinical and scientific input and study design; López-Gómez M developed the study concept, interpreted the data and drafted/edited the manuscript; All authors edited the manuscript.

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