A Population-Based Cross-sectional Study on the Prevalence and Associated Risk Factors of *Helicobacter pylori* Infection in Rafsanjan, a Low Gastric Cancer Area in Southeast Iran

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Abstract

Background:
Despite all improvements in sanitation and exposure to antibiotics over time, *Helicobacter pylori* (HP) prevalence remains high, affecting the lives of about half of the world population, which can gradually lead to serious upper gastrointestinal disorders. Understanding HP's epidemiologic patterns help us to better manage the burden of this infection and to plan more effectively regarding potential screening or eradication strategies. We, therefore, aimed to report the crude and age- and sex-standardized prevalence rate of HP infection, its trend, and possible associated factors among asymptomatic healthy individuals in Rafsanjan city, a low-incidence area of gastric cancer (GC) in the southeast of Iran, from July 2018 to December 2021.

Methods:
This population-based cross-sectional descriptive study included 2,046 male and female subjects between 3 to 72 years who were in good health condition. Study participants were randomly selected from the Health Houses and each underwent a questionnaire-based interview and provided blood and feces samples. The presence of HP infection was detected by serum IgG antibodies and stool antigen test.

Results:
The overall and age- and sex-standardized prevalence rates of HP infection were 50.9% and 43%, respectively. The prevalence rate has notably decreased in all age groups compared with 2007. Also, it was significantly higher among men ($P=0.033$) and increased with advancing age ($P<0.001$). A higher population density living in a specific room area ($P=0.012$) increased the likelihood of HP infection.

Conclusion:
To conclude, the prevalence of HP infection is decreasing over time in Rafsanjan city, which may be due to improvements in living standards in this area. A healthy lifestyle and adherence to hygienic principles, especially during childhood, may be required for a reduction in the prevalence of HP infection.

Keywords:
Prevalence, Epidemiology, *Helicobacter pylori*, Gastric cancer, Rafsanjan, Iran

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Introduction

Helicobacter pylori (HP), a gram-negative, microaerophilic bacterium, colonize the epithelial lining of the human stomach and induce the influx of inflammatory cells into the stomach wall. This pathogen can gradually lead to chronic gastritis, peptic/duodenal ulcer disease, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma.[1] Although gastric carcinogenesis is a multifactorial process, it has been firmly established that the current or past history of HP infection is associated with an increased risk of gastric cancer (GC). So, the global attributable fraction for HP in non-cardia GC is about 89.0%.[2] The International Agency for Research on Cancer (IARC) has also classified HP as a class I carcinogen associated with GC.[3] Therefore, recent interest has focused on HP eradication with a course of antibiotic therapy as a reasonable preventive strategy against GC.[4] HP transmission is typically assumed to take place during early childhood, and most likely interfamilial.[5,6] It usually persists for life unless eliminated by antibiotic treatment. Animals, drinking water supply, and unsanitary environments are other proposed transmission routes.[7-9]

Despite the downward trend in the prevalence of HP infection related to the improved living standards (socioeconomic status, hygiene level, and antibiotics) over time, it remains still high throughout the world. About half of the world's adult population is estimated to be infected with HP infection.[10,11] However, there exists a geographic variation, with a significantly higher prevalence rate in developing countries than in developed ones. Similar to other high-incidence areas of GC, the prevalence of HP is also high among the Iranian population, both adults and children. Based on the estimates of a systematic review and meta-analysis in Iran, the pooled prevalence of HP infection was 42% among children and 62% among adults.[12] Nevertheless, the results of studies addressing the prevalence rate of HP infection in different geographical areas of Iran are inconsistent. This discrepancy may be due to heterogeneities in the HP detection methods, the age distribution of the study populations, and the deprivation of the studied provinces. Although the prevalence of HP infection is high in Iran, there are still doubts about its exact correlation with GC. When we compare the prevalence of HP infection in three distinct areas of Iran with low to high prevalence of GC, as well as in the second and third generations of immigrants from high-(Iran) to low-(Canada) incidence areas,[13] we realize that not all of the HP-infected subjects develop GC, which emphasizes the necessity of the presence of both host-related and environmental factors.[14]

Understanding HP's epidemiologic patterns and recent changes due to improvements in sanitation and exposure to antibiotics helps us to better manage the burden of this infection and to plan more effectively regarding potential screening or eradication strategies. So, this study was designed and conducted to create the framework needed for priority setting in Iran's health policymaking and research in this regard. This cross-sectional population-based study aimed to report the prevalence of HP infection and its possible associated factors among all age groups of asymptomatic healthy individuals in Rafsanjan city, a low-incidence area of GC, located in the Kerman province (Southeastern Iran), from July 2018 to December 2021. Furthermore, we examined the trend by comparing our results with the previous data available from Rafsanjan.

Materials and Methods

Design and Setting

In a descriptive study, we reported the overall and age- and sex-standardized prevalence and determinants of HP infection rate among all age groups of asymptomatic healthy individuals in a low-incidence area of GC in Iran. This study was a population-based cross-sectional study comprising about 2046 Iranians from Rafsanjan city, which aimed to estimate the epidemiology of HP infection using integrated, standardized methods. This project was funded by the National Institute for Medical Research Development (NIMAD) (grant number: 957272). It was first launched in the summer of 2018 with the cooperation of the investigators of the Digestive Diseases Research Institute (DDRI) and the Rafsanjan University of Medical Sciences. The enrollment lasted up to late 2021.

Study Population and Sample Size

Rafsanjan is a county of Kerman province, Southeastern Iran, with near 162 000 estimated inhabitants (2016) and has a generally hot semi-arid climate. This report

is based on about 1.26% of Rafsanjan's population. Overall, 2046 male and female subjects of all age groups who were in good health condition as determined by medical history from both urban and rural regions were included. No exclusion criteria, other than pregnancy, positive history of GC, unwillingness to participate in the study, or having psychological or physical incompetence limiting the possibilities of understanding the requirements for diagnostic and/or medical interventions or confounding the consenting or completion of the questioning process, were used in this study. Study participants were randomly selected from the Health Houses, primary health care centers in Iran containing the information of their covering families and family members.

Data Collection, Variables, and Measurements

The data collection process was summarized as follows: First, the target participants were selected and visited face-to-face by a trained staff member at their homes. After providing an adequate explanation about the aim of the research to the subjects, they were invited to the study sites if they agreed to participate by answering an epidemiological questionnaire and providing blood and feces samples. Furthermore, the study staff member provided the participant with a stool collection kit and instructions and explained the procedure to collect a stool sample at home within 10 hours before the interview visit. On the morning of the visit day, a written informed consent form was obtained initially. If the participants were minors, the guardians or the legally authorized representative provided written informed consent for them. Next, each participant was collected and provided venous blood samples and, for infants and children, only stool samples. Participants were seated in a curtained blood collection office and were asked for a blood sample of about 30 mL (3 test-tube). Samples were obtained using a vacutainer needle (standard method). All samples were prepared, refrigerated, and stored locally and then shipped to DDRI. All the analyses on biological samples were conducted centrally in a standardized manner in a validated reference laboratory at DDRI, Tehran. Finally, each individual underwent an interview and completed a standardized questionnaire regarding the general and medical conditions. The questionnaire explored demographic features, socioeconomic status, gastrointestinal symptoms, clinical history of HP infection, medical history, family history (including GC), personal habits (smoking, alcohol, and drugs), nutritional information, sleeping pattern, and physical activity through self-identification.

The presence of HP infection was detected by IgG antibodies in serum enzyme-linked immunosorbent assay (ELISA) using the commercial HP IgG from Biohit (Helsinki, Finland). HP stool antigen test was also performed using a specific ELISA kit (Pishtazteb Diagnostics). The wealth index was calculated using principal component analysis on the household's possession of durables, access to basic services, and characteristics of the house where living, and then it was categorized into tertiles from poorest to richest.[15] The Room Area was categorized into tertiles from smallest to largest.

The study was coordinated by DDRI. The local investigators at each participating site were responsible for all study activities, coordination, regulatory aspects, and supervision of day-to-day operations. Additionally, a quality assurance and quality control team was assembled to regularly review the data collection procedures. Standardized practices assured high-quality data, and a documental framework was developed for uniform recording and implementation of study activities. Study investigators, coordinators, and all key trained staff members were trained in current Human Subject Protection regulations.

Outcomes and Statistical Analysis

In this study, the primary outcome was to assess the crude and age- and sex-standardized prevalence rate of HP infection among all age groups of asymptomatic healthy individuals in Rafsanjan city, Kerman province, Southeastern Iran. Secondly, the respective figures were specifically explored to determine the potential associated factors.

The database was first structured using Microsoft Office Excel 2016, and all statistical analyses were conducted using Stata/SE version 12 (StataCorp, Texas, USA). The graph was created using Microsoft Office Excel 2016. Frequency and percentage were used as descriptive statistics for categorical variables to summarize the characteristics of the HP-positive and

HP-negative subgroups. For comparison between these subgroups, the chi-square test was used. Moreover, we estimated adjusted prevalence rates of HP infection using the age and sex structure of the Rafsanjan population census in the year 2016. We also visualized the adjusted prevalence rate of HP infection by age in 2007 and 2021 in the Rafsanjan population.

Results

Overall, 2046 participants aged between 3 to 72 years were included whose data were analyzed in this study. The mean±SD age of the study population was 36.09±16.37 years, and 50.7% were female. The overall and age- and sex-standardized prevalence rates of HP infection were 50.9% and 43% (95% CI: 39-45%), respectively. Table 1 shows the HP infection status by sex, age, sociodemographic, sanitary, and lifestyle factors in study participants.

As shown in this table, the prevalence of HP infection was significantly higher among male compared to female subjects (adjusted: 53.3% versus 48.6%, $P=0.033$). Moreover, the prevalence increased with advancing age ($P<0.001$). Regarding room area, a higher population density living in a specific room area increased the likelihood of HP infection ($P=0.012$). There were no significant differences concerning the other variables of the study.

Discussion

In this cross-sectional study in Rafsanjan, a low GC incidence city in Kerman Province, which is in the southeast of Iran, the age and sex-standardized prevalence of HP infection in individuals (aged 3-72 years) in 2021, was 43%. Also, the prevalence of HP infection in children 1 to 10 years old was 9.5%. In our study, this prevalence was significantly higher among male subjects ($P=0.033$) and increased with advancing age ($P<0.001$). A higher population density living in a specific room area ($P=0.012$) increased the likelihood of HP infection. There were no significant differences concerning the other variables Wealth Score Index (WSI), water source, smoking, denture, and animal contact) of the study.

Given the health consequences caused by HP infection, it is pivotal to understand its prevalence and trend in a population to implement effective preventive

Table 1. Associated factors with the HP infection prevalence in Rafsanjan city, Iran, from 2018 and 2021 (n=2046)

Variables	Levels	Negative No. (%)	Positive No. (%)	*P* value*
Sex	Male	471 (46.7)	537 (53.3)	0.033
	Female	534 (51.4)	504 (48.6)	
Age	0-12	109 (90.8)	11 (9.2)	<0.001
	13-40	655 (54.5)	546 (45.5)	
	40+	241 (33.2)	484 (66.8)	
WSI	Low	121 (33.9)	236 (66.1)	0.148
	Medium	126 (37.7)	208 (62.3)	
	High	99 (41.8)	138 (58.2)	
Room area	Small	123 (37.0)	209 (63.0)	0.012
	Medium	90 (31.3)	198 (68.8)	
	Large	133 (43.0)	176 (57.0)	
Water source	History of other sources	144 (52.2)	278 (50.9)	<0.733
	Tap water	132 (47.8)	268 (49.1)	
Smoke, Hookah, drug	No	199 (58.5)	306 (63.5)	<0.151
	Yes	141 (41.5)	176 (36.5)	
Denture	No	195 (70.9)	358 (65.4)	<0.115
	Yes	80 (29.1)	189 (34.6)	
Animal contact	No	35 (12.6)	59 (10.7)	<0.420
	Yes	242 (87.4)	490 (89.3)	

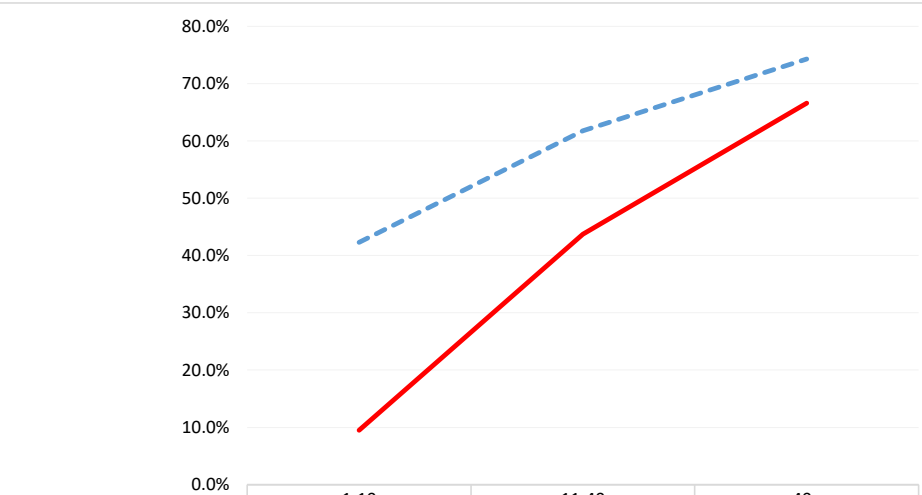
* Based on chi-square test.

strategies.[16,17] The global prevalence of HP infection is high, and about half the world's population is infected with HP infection.[11,18,19] A systematic review and meta-analysis by Hooi and colleagues regarding the prevalence of HP infection in 2015 showed that Africa had the highest pooled prevalence (79.1%), Asia had a prevalence of 54.7%, and Oceania had the lowest prevalence (24.4%).[11]

The prevalence of HP infection varies geographically in Iran and has been reported to be between at least 36% and as high as 90%.[19] In a study by Maleki et al in individuals aged between 15 and 65 years in Sari, northern Iran, the prevalence of HP infection was 44.5%.[20] Based on the results of the study done by Salehi and colleagues, The prevalence of HP infection in Neyshabur, northeastern Iran, was high in the healthy population, as the overall IgA, IgG, and IgM seropositive samples among the study participants were 7.2%, 72.8%, and 5.2%, respectively.[21] The study by Jafarzadeh et al showed that the seroprevalence of HP infection in healthy adults and children was 67.5% and 46.6%, respectively.[22] Another study by the same authors in Rafsanjan in 2013 reported that the overall seroprevalence of anti-HP IgG antibodies in healthy subjects was 75% (Figure 1),[23] while our findings in 2021 presented that the age and sex-standardized prevalence of HP infection in individuals aged 3-72 years in Rafsanjan was %43. The prevalence appears to have decreased over time in Rafsanjan.

Also, our findings reveal that the prevalence of HP infection in children 1 to 10 years old was 9.5%, while in a study by Ghasemi-Kebria et al in 2009 on healthy children (1-15 years) of Golestan province, a region with a high prevalence in Iran, seroprevalence was 50.5%.[24] In the study by Soltani and colleagues the prevalence of HP infection was very high (64.2%) among children in Sanandaj, western Iran.[25] In another study in Shiraz, southern Iran, the prevalence of HP infection in neonates, children aged 6 months to 3 years, and 10- and 15-year-old children were 25%, 22%, 19.5%, and 29.2%, respectively.[17]

The risk factors for HP infection have been investigated in some studies. Sex, age, number of family members, education, marital status, sources of drinking water, alcohol consumption, and habit of hand washing before the meal were identified as risk factors for HP infection.[25-27] The results of this study are consistent with some studies and showed that the prevalence of HP infection was significantly higher in male compared with female subjects.[22,28,29] It seems that male subjects are more susceptible to infection compared with female subjects. In a study by Ashtari et al the prevalence of HP infection decreased by age.[27] In contrast, our study showed that the prevalence of HP infection increased with advancing age, similar to other studies.[26,28] It seems reasonable to assume that HP infection begins at infancy



	1-10	11-40	40+
HP prevalence (2007)	42.3%	61.8%	74.3%
HP prevalence (2021)	9.5%	43.7%	66.6%

Figure 1. The adjusted prevalence of HP infection by age in 2007 and 2021 in the Rafsanjan population.

and cumulatively increases with age.

In our study, a higher population density living in a specific room area had a positive association with HP infection. Although the transmission route is still unclear (possibly by oral-oral or fecal-oral route), our data confirmed previous studies that HP infection was more common among individuals living in crowded houses.[30-33]

In previous studies, poor tooth brushing habits had been determined as possible risk factors for HP infection.[34] Similarly, Moreira and colleagues have found a strong association between brushing the teeth more than once daily with HP infection.[35]

Conclusion

According to the results of this study, the prevalence of HP infection is decreasing over time in Rafsanjan, southeastern Iran, which may be due to improvements in living standards in this area. A healthy lifestyle and adherence to hygienic principles, especially during childhood, may be required for a reduction in the prevalence of HP infection in younger and middle-aged individuals.

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Ethical Approval

The study protocol was approved by the Ethics Committee of the NIMAD (IR.NIMAD.REC.1396.062) and was conducted per the Declaration of Helsinki.

Conflict of Interest

The authors declare no conflict of interest related to this work.

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