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Alimentary Tract

Smoking increases the likelihood of *Helicobacter pylori* treatment failure

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ABSTRACT

Background and aims: Data regarding the impact of smoking on the success of *Helicobacter pylori* (*H. pylori*) eradication are conflicting, partially due to the fact that sociodemographic status is associated with both smoking and *H. pylori* treatment success. We aimed to assess the effect of smoking on *H. pylori* eradication rates after controlling for sociodemographic confounders.
Methods: Included were subjects aged 15 years or older, with a first time positive C^{13}-urea breath test (C^{13}-UBT) between 2007 to 2014, who underwent a second C^{13}-UBT after receiving clarithromycin-based triple therapy. Data regarding age, gender, socioeconomic status (SES), smoking (current smokers or "never smoked"), and drug use were extracted from the Clalit health maintenance organization database.
Results: Out of 120,914 subjects with a positive first time C^{13}-UBT, 50,836 (42.0%) underwent a second C^{13}-UBT test. After excluding former smokers, 48,130 remained who were eligible for analysis. The mean age was 44.3 ± 18.2 years, 69.2% were females, 87.8% were Jewish and 12.2% Arabs, 25.5% were current smokers. The overall eradication failure rates were 33.3%: 34.8% in current smokers and 32.8% in subjects who never smoked. In a multivariate analysis, eradication failure was positively associated with current smoking (Odds Ratio {OR} 1.15, 95% CI 1.10–1.20, $p < 0.001$), female gender (OR 1.20, 95% CI 1.14–1.25, $p < 0.001$) and a low socioeconomic status (OR 1.24, 95% CI 1.17–1.31, $p < 0.001$).
Conclusions: After controlling for socio-demographic confounders, smoking was found to significantly increase the likelihood of unsuccessful first-line treatment for *H. pylori* infection.

1. Introduction

Helicobacter pylori (*H. pylori*) is the most common chronic pathogen in humans [1–3] and the leading cause of peptic ulcer disease and gastric malignancy [3,4]. Hence, *H. pylori* eradication has paramount significance in preventing and treating these illnesses.

H. pylori eradication is unsuccessful in approximately 7–28% of cases [5–7] and is related to both host and bacterial factors [2,8–11]. Treatment failure may be due to antibiotic drug resistance, pharmacodynamic and pharmacokinetic effects, drug-drug interactions, bacterial virulence factors, and poor compliance [2,10,12]. Repeated treatment attempts represent a significant public health burden, and for this reason attempts have been made to identify host factors which may identify those at increased risk of treatment failure so that steps can be taken to optimize treatment [7,13].

Among host-related factors, smoking has been studied as a possible risk factor for eradication failure. The most extensive data to date comes from a meta-analysis of 22 studies including 5538 patients in which the odds ratio for eradication failure in smoking patients was 1.95 compared to non-smokers [7]. However, in this meta-analysis there was no differentiation between current or past smoking. Furthermore, the studies that were included were conducted in various countries, where different *H. pylori* strains and drug resistance patterns may have influenced the eradication rates.

In addition, sociodemographic parameters are known to be related to both differential *H. pylori* prevalence as well as smoking status. The fact that both *H. pylori* infection and smoking are associated with lower socioeconomic strata of the population makes it difficult to isolate the effect of smoking on *H. pylori* treatment, and therefore limits the quality of previous studies [13–17].

In this study, we aimed to evaluate the effect of current smoking on *H. pylori* eradication failure rate after controlling for sociodemographic parameters in a single country cohort.

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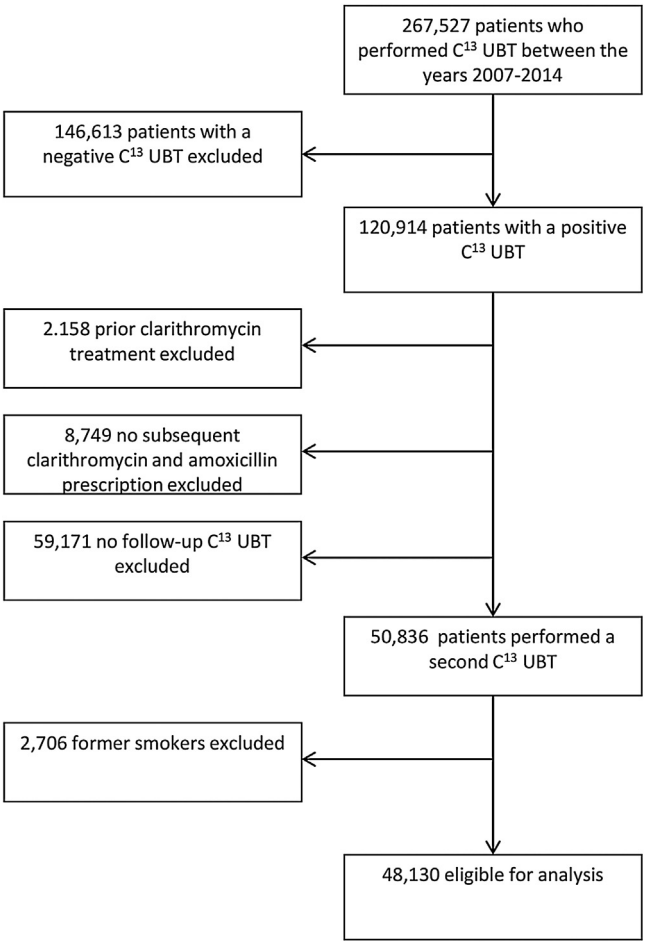

Fig. 1. Patient selection. Abbreviation: C^{13}-UBT—C^{13}-urea breath test.

2. Methods

2.1. Study population

Data was extracted from the database of Clalit health services (CHS), the largest health provider in Israel [14]. First, we identified all patients aged 15 years or older who had a positive C^{13}-urea breath test result (C^{13}-UBT) for the detection of *H. pylori* infection between the years 2007–2014 (Fig. 1). Second, we excluded patients who had been prescribed clarithromycin within 5 years prior to the index C^{13}-UBT in order to ensure only naïve patients were included. Finally, we selected only the patients who were prescribed clarithromycin and amoxicillin within 3 months of the index C^{13}-UBT and underwent a second C^{13}-UBT. This study design ensured that only patients who were receiving first line treatment were included for analysis. Two study investigators (D.I. and H.L) randomly selected 100 patients and performed an independent manual check of electronic medical records, which verified that all patients were treatment naïve before receiving first line triple therapy with a proton pump inhibitor (PPI), amoxicillin and clarithromycin (100% accuracy and 100% concordance).

2.2. C^{13}-urea breath testing

Breath tests were collected by dedicated nurses in community CHS clinics. Patients were given 75 mg of C^{13} labeled urea mixed with 100 mL of orange juice. Breath samples were collected at two intervals—prior to urea administration (T0) and 30 minutes post urea administration (T30). The T0 and T30 collection tubes samples (Vacutainer, Becton, Dickinson and Company, NJ, USA), were sent to our laboratory for C^{13} UBT analysis for diagnosis of *H. pylori* infection. The tubes were analyzed by isotope ratio mass spectrometer (IRMS) instruments (AP2003, Analytical Precision, UK).

The results are expressed as the difference between the two scores—delta over baseline. The cut-off $\frac{C13}{C12}$ at T30-T0 was 3.5 parts per thousand (PPT), according to referral laboratories and the manufacturer's instructions. Any increase greater than 3.5 PPT was considered positive for *H. pylori*.

Prior to UBT, as part of the protocol, a dedicated nurse proactively verified that PPI was stopped for at least 10 days.

2.3. Data extraction

Following the identification of patients, we electronically retrieved the following sociodemographic data from the CHS database: socioeconomic status (SES), clinic address, age, gender, smoking status and ethnicity.

SES was derived by means of geocoding technique, by linking the address of the primary care clinic serving the individual with the census area-level SES data, based on the ratings of the Israel's Central Bureau of Statistics [15]. SES was rated in a scale of 1–10, where grade 1 corresponds to the lowest SES score and grade 10 corresponds to the highest SES score. We subdivided SES into three categories: low (SES score 1–3), intermediate (SES score of 4–6) and high (SES score of 7–10).

Smoking status was electronically recorded by the primary care physician and patients were categorized as either current smokers, former smokers or as "never-smoked". In order to minimize the confounding effects of past smoking, former smokers were excluded from the final data set.

2.4. Statistical analysis

All analyses were performed using SPSS version 22.0 statistical analysis software (IBM Inc, Chicago, IL, USA). Distributions of continuous variables were assessed for normality using the Kolmogorov–Smirnov test (cutoff at $p < 0.01$) and were described as mean ± standard deviation. Continuous variables were compared by antibiotic susceptibility using the t-test for independent samples or the Mann Whitney U as appropriate. Nominal variables were described as frequency counts and presented as N(%). Nominal variables were compared by using the chi square test. Multivariate forward logistic regression model was used in the statistical analysis to estimate odds ratios (OR) and 95% confidence interval. All tests were two-sided and considered significant at $p < 0.05$.Since clarithromycin resistance data was unavailable in our cohort, we repeated the multivariate analysis with random allocation of 22% in accordance with the presumed clarithromycin resistance in Israel [16]. The multivariate analysis with random allocation was bootstrapped 1000 times.

The research was approved by the institutional Helsinki ethics committee of Rabin Medical Center.

3. Results

A total of 120,914 patients with a positive first time C^{13}-UBT were identified. 50,836 (42.0%) underwent a second C^{13}-UBT. After excluding former smokers, 48,130 patients remained who were eligible for analysis (Fig. 1). The mean age of the study population was 44.2 ± 18.2 years and 33,305 (69.2%) were female. Patient characteristics are displayed in Table 1.

Overall, *H. pylori* eradication failed in 16,041(33.3%) patients. Failure of *H. pylori* eradication was more likely in current smokers compared to patients who had never smoked (4218 (34.8%) and 11,823 (32.8%), $p < 0.001$, respectively). In a univariate analysis, *H.*