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Systemic Metabolic and Inflammatory Changes Associated with *Helicobacter Pylori* Eradication: A Controlled Before–after Cohort Comparing Eradication Success and Persistent Infection

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ABSTRACT

Background & Aims: *Helicobacter pylori* (*H. pylori*) infection has been linked to systemic metabolic and inflammatory disturbances beyond the gastric mucosa, yet evidence regarding biomarker changes after eradication remains heterogeneous. This study evaluated systemic metabolic and inflammatory changes associated with eradication success versus persistent infection, using *H. pylori*–negative controls within a controlled before–after cohort framework.

Methods: Adults undergoing stool *H. pylori* antigen testing at a tertiary referral center in Türkiye (2020–2025) with paired baseline (pre) and follow-up (post) laboratory measurements were included. Participants were classified as *H. pylori*–negative controls, eradication success (baseline positive, follow-up negative), or eradication failure (baseline and follow-up positive). Co-primary endpoints were follow-up HOMA-IR and hsCRP (log-transformed), compared between groups using ANCOVA adjusted for baseline values and prespecified covariates. Prespecified supportive analyses used a difference-in-differences framework. Secondary outcomes included glycemic measures, lipid profile, hematological inflammation indices, and liver-related biomarkers; TyG index and FIB-4 were assessed exploratorily.

Results: A total of 3,756 individuals were included (1,321 controls; 1,847 eradication success; 588 eradication failure). In adjusted analyses, eradication success showed a more favorable follow-up profile with lower insulin resistance and systemic inflammation compared with controls, whereas eradication failure showed an opposing pattern. Directionally consistent differences were also observed across secondary metabolic, inflammatory, and hepatic biomarkers and were supported by difference-in-differences analyses.

Conclusions: Compared with *H. pylori*–negative controls, eradication success was associated with a more favorable systemic short-term metabolic–inflammatory profile, whereas persistent infection tended to show the opposite pattern. Prospective studies with longer follow-up are needed to determine durability and clinical relevance.

Key words: *Helicobacter pylori* – eradication – insulin resistance – high-sensitivity C-reactive protein – systemic inflammation – metabolic dysfunction-associated steatotic liver disease.

Abbreviations: BMI: body mass index; CRP: C-reactive protein; DM: diabetes mellitus; FDR: false discovery rate; FIB-4: Fibrosis-4; HbA1c: glycated hemoglobin; HOMA-IR: homeostatic model assessment of insulin resistance; *H. pylori: Helicobacter pylori*; hsCRP: high-sensitivity CRP; NLR: neutrophil-to-lymphocyte ratio; OAD: oral antidiabetic drug; PLR: platelet-to-lymphocyte ratio; PPI: proton pump inhibitor; TyG: triglyceride–glucose.

INTRODUCTION

Helicobacter pylori (*H. pylori*) management is increasingly framed not only around gastroduodenal disease but also around potential extra-gastric consequences, as chronic infection can generate a persistent low-grade inflammatory milieu with plausible metabolic downstream effects. Contemporary guidelines emphasize confirming active infection, providing effective eradication therapy, and performing test-of-cure, creating an opportunity to evaluate systemic biomarker trajectories in a standardized clinical workflow [1, 2].

Consistent with this concept, observational evidence links *H. pylori* infection to adverse cardiometabolic patterns, including insulin resistance/metabolic syndrome and

dyslipidemia [3, 4]. However, post-eradication changes in systemic inflammation and metabolic indices remain inconsistent across studies, partly due to heterogeneity in diagnostic methods, follow-up timing, and analytical strategies. For example, a meta-analysis suggested a reduction in circulating C-reactive protein (CRP) after eradication but highlighted limited and heterogeneous evidence [5], while prospective data in metabolic liver disease contexts have reported improvements in inflammatory and metabolic markers over longer follow-up intervals [6, 7]. Longitudinal studies further suggest that persistent (ongoing active) *H. pylori* infection may be particularly relevant for incident metabolic dysfunction-associated steatotic liver disease (MASLD) risk, underscoring the importance of differentiating eradication success from persistent infection rather than treating all treated patients as a homogeneous group [8]. Likewise, large cohort data indicate that eradication may reduce subsequent dyslipidemia risk compared with persistent infection [9]. Collectively, these observations motivate controlled before–after evaluations that compare eradication success versus failure while incorporating an *H. pylori*–negative comparator group assessed over a similar interval, to better distinguish treatment-related effects from time-dependent variation.

The aim of this study was to evaluate changes in systemic metabolic and inflammatory profiles following H. pylori eradication using a broad panel of biomarkers. Our primary hypothesis was that successful eradication would be associated with improvements in insulin resistance (HOMA-IR) and systemic inflammation [high-sensitivity CRP (hsCRP)], whereas persistent infection would show a less favorable biomarker trajectory. Secondary outcomes included glycemic measures (fasting glucose, fasting insulin, glycated hemoglobin (HbA1c)], lipid profile, hematological inflammation indices [neutrophil-to-lymphocyte ratio (NLR) / platelet-to-lymphocyte ratio (PLR)] and selected biochemical markers; in exploratory analyses, we additionally evaluated the triglyceride–glucose (TyG) index and the Fibrosis-4 (FIB-4) score as pragmatic surrogate indices related to cardiometabolic risk and MASLD.

METHODS

This retrospective cohort study used a controlled before–after design, conducted using observational data at a tertiary teaching and research hospital in Türkiye. The study reporting was planned in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) principles.

The study was conducted at a tertiary teaching and research hospital in the Departments of Internal Medicine, Gastroenterology, and Nephrology. Data were retrospectively obtained from the hospital information system and laboratory information system. The data coverage period was 2020–2025; data from 2021 were not included in the dataset due to a marked decrease in outpatient visits during the COVID-19 pandemic, interruptions in follow-up processes, and limitations regarding data integrity.

A total of 4,500 patients who underwent stool antigen testing for H. pylori were screened. The variables included in the analysis and pre/post measurements were obtained from laboratory tests requested as part of routine clinical follow-up.

The study was conducted within an observational analytical framework aimed at evaluating the relationship between *H. pylori* status and eradication success with short-term metabolic and inflammatory biomarkers. Time zero (baseline) was defined as the period when baseline (pre) laboratory measurements were taken and *H. pylori* status was assessed. Outcomes were evaluated based on post measurements obtained within the defined follow-up window. Due to the observational design of the study, results were interpreted at the level of association rather than causal effect.

The request for *H. pylori* testing was made by the relevant physician based on upper gastrointestinal complaints (epigastric pain, dyspepsia, bloating, suspected gastritis/ulcer, etc.) and clinical risk assessment (e.g., planned nonsteroidal anti-inflammatory drugs or aspirin use or concomitant ulcer risk factors) in routine clinical practice. The study population consisted of cases who presented to the same institution during the same period and for whom an *H. pylori* stool antigen test was requested.

Inclusion criteria were: 1) documented *H. pylori* stool antigen test result; 2) availability of study panel measurements at both baseline (pre) and follow-up (post) time points for the same individual; 3) recorded follow-up duration (weeks); 4) age ≥ 18 years. Exclusion criteria were missing any variable in the study panel at either the pre- or post-time point, absence of follow-up duration records, age <18 years, and excessively short or excessively long follow-up durations evaluated in a priori sensitivity analyses.

Helicobacter pylori status and eradication success were defined according to test results recorded in the laboratory information system:

- Hp (+) eradication success group: initial test positive, follow-up test negative;
- Hp (+) eradication failure group: initial test positive, follow-up test positive;
- Hp (–) control group: initial test negative; negative at follow-up time point.

The Hp (–) control group was formed from individuals who presented with similar clinical complaints at the same institution during the same period, for whom a stool antigen test was requested and found to be negative. Post-measurements in the control group were taken from the first appropriate laboratory panel obtained during routine clinical follow-up within the defined follow-up window after the pre-measurement. The Hp (–) control group was treated as a reference group representing time-dependent change; between-group effects were estimated using models adjusted for the corresponding baseline value.

Detection of *H. pylori* stool antigen was performed using a commercially available fluorescence immunoassay (FIA) kit (STANDARD F *H. pylori* Ag FIA; SD BIOSENSOR, Republic of Korea). This cassette-based assay provides qualitative results from fecal specimens. The test membrane is precoated with a monoclonal anti–*H. pylori* flagellar antibody at the test line, and results were interpreted after approximately 10 minutes as positive or negative for *H. pylori* antigen. As this was a retrospective study based on routine clinical care,

local diagnostic accuracy validation against an independent reference standard was not performed. Routine internal quality-control procedures were implemented according to the manufacturer's recommendations; therefore, test results should be interpreted within the context of routine clinical practice.

Eradication therapy was organized in accordance with routine clinical practice. Quadruple therapy regimens containing bismuth are predominantly used in institutional practice, with a standard treatment duration of 14 days. Follow-up (second test) stool antigen testing was requested in routine clinical practice at least 6 weeks after the start of treatment. Considering the treatment duration, this approach corresponds to the control test being performed at least 4 weeks after the end of treatment.

In line with the guideline recommendations, discontinuation of proton pump inhibitor (PPI) use prior to the validation test was targeted; however, the timing of PPI discontinuation could not be confirmed in a structured manner in all cases on a patient-by-patient basis. To reduce this potential risk of misclassification, PPI use was included as a covariate in the models; in addition, a sensitivity analysis excluding PPI users was planned a priori and implemented.

Medication use variables [statin, oral antidiabetic drugs (OAD), PPIs] were defined based on active prescription/medication use records close to the pre-measurement time. As medication changes during follow-up could not be monitored in a structured manner in all cases, changing medication use over time was assessed as a potential confounder within limitations.

Pre-measurements are laboratory results closest to the baseline period. Post-measurements are control laboratory results within the defined follow-up window during the follow-up period.

Blood samples were collected in BD brand gel tubes, and serum was obtained by centrifuging at 2000G for 10 minutes after clotting. Urea, creatinine, sodium, potassium, and other routine biochemical parameters were analyzed using a photometric method on an autoanalyzer device (Abbott Architect ci16200, USA). Hemogram measurements were performed on automatic analyzers in accordance with the institution's standard workflow.

High-sensitivity CRP was used as a marker of systemic inflammation. The hsCRP measurement was performed on the Siemens BN II/BN ProSpec platform using the particle-enhanced immunonephelometry principle (CardioPhase hsCRP reagent; results in mg/L). Since hsCRP can exhibit a right-skewed distribution, log transformation was applied in the analyses (log-hsCRP).

Glycated hemoglobin measurement was performed using the ion-exchange high-performance liquid chromatography (HPLC) method on whole blood (Tosoh HLC-723 G8, Tosoh Bioscience, Japan). Fasting glucose and fasting insulin were obtained from measurements recorded as 'fasting' in the hospital information system/laboratory information system. Due to the retrospective design, individual fasting duration and sample collection times could not be verified in all cases; this limitation was considered in the interpretation of the results.

NLR and PLR were defined as the neutrophil/lymphocyte and platelet/lymphocyte ratios, respectively. HOMA-IR was calculated using the standard formula: HOMA-IR = (fasting glucose [mg/dL] × fasting insulin [μIU/mL]) / 405.

Co-primary endpoints were:

Insulin resistance at follow-up (HOMA-IR_post), compared between groups using ANCOVA with baseline HOMA-IR_pre as a covariate.

Systemic inflammation at follow-up (hsCRP_post, analysed on the log-transformed scale), compared between groups using ANCOVA with baseline hsCRP_pre (log-transformed) as a covariate.

Additionally, TyG index and FIB-4 were assessed as exploratory secondary measures related to MASLD-associated metabolic risk and interpreted cautiously given the retrospective design. TyG was calculated as ln[fasting triglycerides (mg/dL) × fasting glucose (mg/dL) / 2], and FIB-4 as age (years) × AST (U/L) / [platelets (10^9/L) × $\sqrt{}$ALT (U/L)].

Secondary endpoints were glycaemic parameters: fasting glucose, fasting insulin, HbA1c; lipid profile: total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides; hematological inflammation indices: NLR, PLR; other biochemistry/hematology: neutrophils, lymphocytes, platelets, AST, ALT, GGT, hemoglobin, albumin, ferritin, vitamin B12, 25(OH)D vitamin, uric acid, creatinine.

Predefined covariates: age, gender, body mass index (BMI); diabetes mellitus (DM) and prediabetes status; statin use; OAD use; PPI use; follow-up duration (weeks).

Diabetes mellitus and prediabetes classification was performed in accordance with hospital information system diagnosis records and/or antidiabetic treatment records, considering biochemical thresholds. Prediabetes was defined as HbA1c 5.7–6.4% and/or fasting glucose 100–125 mg/dL; DM was defined as HbA1c ≥6.5% and/or fasting glucose ≥126 mg/dL and/or diagnosis/treatment record. Variable names in the dataset were standardized prior to analysis.

Data cleaning and consistency checks were performed prior to analysis. Derived indices (HOMA-IR, NLR, PLR) were recalculated from component variables and compared with recorded values; variable names and unit consistency were standardized. Values outside biologically plausible ranges were excluded from the analysis when identified as erroneous records after validation. Log transformation was used for hsCRP due to its distribution characteristics.

Statistical Analysis

Continuous variables were summarized by mean ± standard deviation or median (IQR) according to distribution; categorical variables were summarized by number (%). Baseline characteristics between groups were reported for descriptive purposes. The ANCOVA approach was used for co-primary endpoints. The dependent variable post-measurement value was included in the model along with the baseline (pre) level, group variable, and pre-specified covariates. Model for HOMA-IR: HOMA_IR_post ~ HOMA_IR_pre + group + age + gender + BMI + DM + prediabetes + statin + OAD + PPI + follow-up duration (weeks). Model for hsCRP (with log transformation): log(hsCRP_post) ~ log(hsCRP_pre) + group + age + gender + BMI + DM + prediabetes + statin + OAD + PPI + follow-up duration (weeks). Due to co-primary endpoints (two endpoints), the family-level type-I error rate was controlled

using the Holm–Bonferroni method, and adjusted p-values were reported for co-primary analyses.

To support the controlled before–after design, difference-in-differences models including group×time interaction were applied; within-subject correlation was accounted for using cluster-robust standard errors. Models were adjusted for age, gender, BMI, DM, prediabetes, statin, OAD, PPI, and follow-up duration.

Multiple comparison adjustment for secondary endpoints was performed using the false discovery rate (FDR) (Benjamini–Hochberg) method. Co-primary endpoints were excluded from this scope (assessed using Holm–Bonferroni).

The distribution of model residuals and variance homogeneity were assessed using visual methods. Heteroscedasticity-robust standard errors were used where necessary. Effect sizes were reported as beta coefficients and 95% confidence intervals.

To standardize the follow-up period, analyses limited to the 8–12 week range, analyses excluding PPI users, re-analyses in non-DM individuals, and stratified analyses by statin use were planned and performed a priori to assess interactions.

All analyses were performed using Python 3.11 with pandas 2.2.2, statsmodels 0.14.2, numpy 1.26.4, and scipy 1.12.0. The pandas and statsmodels packages were used for data management and statistical modelling, respectively. The analysis workflow and output tables were archived for reproducibility.

Ethical Approval and Confidentiality

The study was approved by the institutional ethics committee (Decision date: 16 December 2025; Decision no: 2025/70). The data were anonymized by removing identifying information prior to analysis and were used solely for scientific research purposes

RESULTS

A total of 4,500 patients who underwent *H. pylori* assessment via stool antigen testing during the study period were screened. A total of 3,756 patients who met the criteria of having a complete study panel at both pre- and post-time points and having a recorded follow-up period were included in the analysis. The included patients were divided into three groups: Hp− control (n=1321), Hp+ eradication success (n=1847), and Hp+ eradication failure (n=588). Patient flow is presented in Fig. 1.

The mean ages of the groups were similar (Hp− control 50.7±19.3; Hp+ eradication success 51.0±19.2; Hp+ eradication failure 50.8±19.7 years), and the proportions of women were comparable (58.0%, 59.1%, and 61.2%, respectively). The mean BMI ranged from 27.8 to 28.4 kg/m². Diabetes mellitus prevalence was higher in the Hp+ eradication failure group (Hp− 31.1%; Hp+ eradication success 26.2%; Hp+ eradication failure 34.4%). Follow-up duration was similar across groups (median 9.9–10.1 weeks; IQR approximately 8.0–12.0 weeks). Baseline HOMA-IR was higher in the Hp+ eradication failure group (median: Hp− 2.97; Hp+ eradication success 2.79; Hp+ eradication failure 3.12), whereas baseline hsCRP was similar across groups (median, mg/L: Hp− 2.37; Hp+ eradication success 2.53; Hp+ eradication failure 2.67). Detailed baseline characteristics are summarized in Table I.

Eradication success did not differ by statin use: success was 77.1% among statin users versus 75.4% among non-users (p=0.405). In adjusted logistic regression (age, sex, BMI, diabetes/prediabetes, OAD, PPI, follow-up duration), statin use was not associated with eradication success (OR=1.11; 95%CI: 0.90–1.36; p=0.343).

In covariate-adjusted analyses, follow-up HOMA-IR was significantly lower in the Hp+ eradication success group and significantly higher in the Hp+ eradication failure group relative to Hp− controls; follow-up HOMA-IR was also significantly lower in the eradication success group than in the eradication failure group (all p<0.001; Table II; Fig. 2A). Unadjusted analyses were directionally consistent.

Adjusted analyses showed a more favorable follow-up hsCRP profile in the eradication success group and a less favorable profile in the eradication failure group relative to Hp− controls; eradication success also differed significantly from eradication failure (all p<0.001; Table II).

Multiple comparison correction for co-primary endpoints was applied using the Holm–Bonferroni method, and the results for both co-primary endpoints remained statistically significant after correction (Table II).

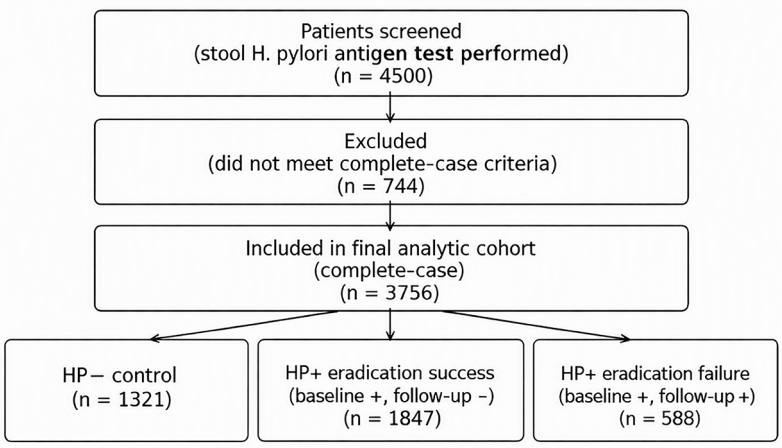


Fig. 1. Study flow diagram.

Table I. Baseline characteristics

Variable	Hp− control (n=1321)	Hp+ eradication success (n=1847)	Hp+ eradication failure (n=588)
Age, years	50.7 ± 19.3	51.0 ± 19.2	50.8 ± 19.7
Female sex, n (%)	766 (58.0%)	1091 (59.1%)	360 (61.2%)
BMI, kg/m²	28.2 ± 5.0	27.8 ± 4.9	28.4 ± 5.0
Diabetes mellitus, n (%)	411 (31.1%)	484 (26.2%)	202 (34.4%)
Prediabetes, n (%)	302 (22.9%)	490 (26.5%)	157 (26.7%)
Statin use, n (%)	397 (30.1%)	544 (29.5%)	162 (27.6%)
Oral antidiabetic drug use, n (%)	279 (21.1%)	324 (17.5%)	131 (22.3%)
Proton pump inhibitor use, n (%)	467 (35.4%)	616 (33.4%)	231 (39.3%)
Follow-up duration, weeks, median (IQR)	9.9 (7.9–12.1)	9.9 (8.0–12.0)	10.1 (8.0–12.0)
HOMA-IR (pre), median (IQR)	2.97 (1.95–4.42)	2.79 (1.89–4.39)	3.12 (2.12–4.52)
hsCRP (pre), mg/L, median (IQR)	2.37 (1.52–3.93)	2.53 (1.61–4.07)	2.67 (1.62–4.15)
HbA1c (pre), %, mean ± SD	6.31 ± 0.99	6.22 ± 0.95	6.38 ± 0.99
Fasting glucose (pre), mg/dL, median (IQR)	108.4 (94.8–126.0)	107.2 (95.0–121.8)	112.0 (96.3–129.9)
Fasting insulin (pre), µIU/mL, median (IQR)	11.09 (7.79–15.37)	10.70 (7.38–15.73)	11.07 (8.10–16.40)
Total cholesterol (pre), mg/dL, mean ± SD	193.1 ± 53.7	190.5 ± 51.4	196.1 ± 52.3
LDL-C (pre), mg/dL, mean ± SD	114.9 ± 42.1	113.6 ± 40.8	117.6 ± 42.5
HDL-C (pre), mg/dL, mean ± SD	47.2 ± 12.3	47.7 ± 12.1	46.9 ± 12.2
Triglycerides (pre), mg/dL, median (IQR)	156.2 (115.9–213.0)	151.8 (111.1–210.8)	160.8 (118.1–216.8)
NLR (pre), median (IQR)	2.15 (1.62–2.91)	2.16 (1.61–2.95)	2.16 (1.63–2.91)
PLR (pre), median (IQR)	125.0 (97.0–160.9)	123.0 (95.7–160.6)	127.8 (98.7–163.0)

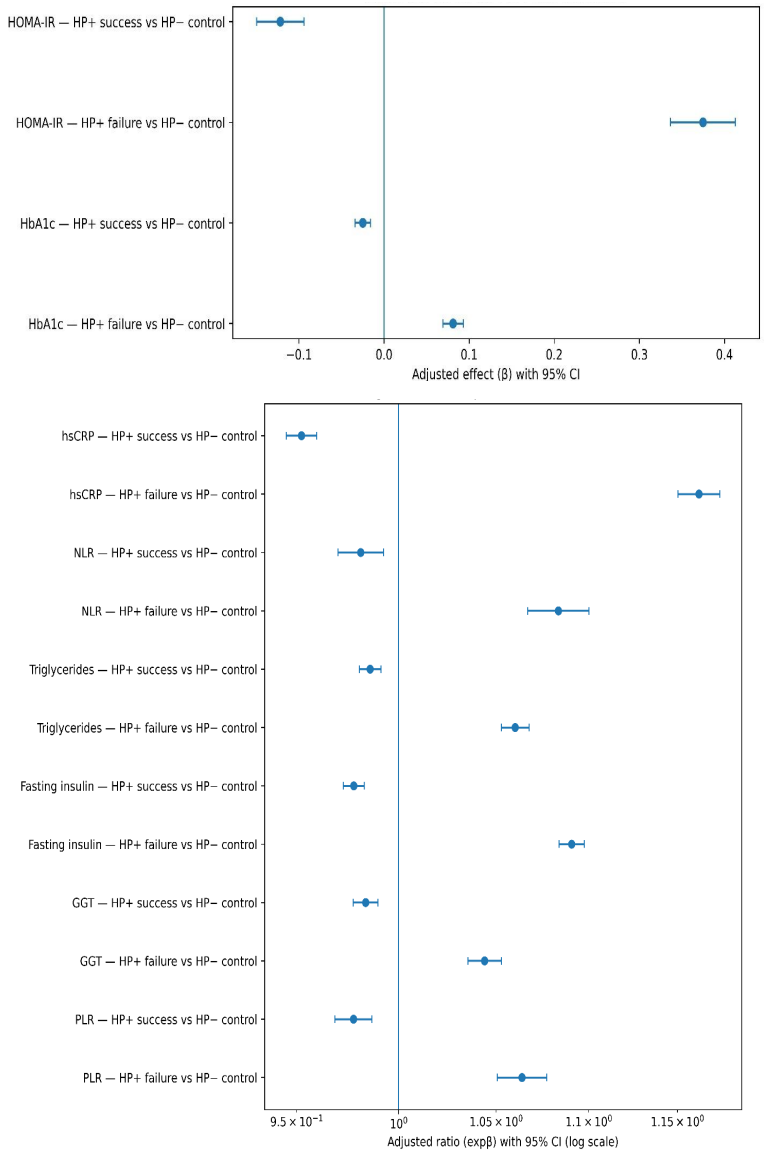
Values are mean ± SD for approximately normally distributed variables and median (IQR) for skewed variables. *Hp: Helicobacter pylori*; BMI: body mass index; hsCRP: high-sensitivity C-reactive protein; HOMA-IR: homeostatic model assessment of insulin resistance; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.

Secondary endpoints were evaluated exploratorily, and FDR control was applied (Table III). In exploratory adjusted analyses, TyG showed a more favorable profile in the eradication success group and a less favorable profile in the eradication failure group, with significant differences across all main contrasts (Table III). In contrast, FIB-4 differences were small and should be interpreted cautiously; although eradication success differed modestly from controls and from eradication failure, the absolute magnitude of this signal was limited (Table III). Overall, an opposite and consistent pattern was observed between the Hp+ eradication success and Hp+ eradication failure groups. In glucose metabolism parameters, the Hp+ eradication success group showed lower fasting glucose and fasting insulin levels and a small decrease in HbA1c, whereas the Hp+ eradication failure group showed higher levels of the same parameters (Table III).

Table II. Co-primary outcomes: adjusted associations from ANCOVA models (HC3 robust standard errors)

Outcome / model	Comparison	Adjusted effect (95% CI)	p value (raw)	p value (Holm-adjusted)*
HOMA-IR (ANCOVA)	Hp+ eradication success vs Hp− control	β = −0.122 (−0.150 to −0.094)	<0.001	<0.001
HOMA-IR (ANCOVA)	Hp+ eradication failure vs Hp− control	β = 0.375 (0.337 to 0.413)	<0.001	<0.001
HOMA-IR (ANCOVA)	Hp+ eradication success vs Hp+ eradication failure	β = −0.497 (−0.533 to −0.460)	<0.001	<0.001
hsCRP (log-ANCOVA)	Hp+ eradication success vs Hp− control	expβ = 0.952 (0.945 to 0.960)	<0.001	<0.001
hsCRP (log-ANCOVA)	Hp+ eradication failure vs Hp− control	expβ = 1.162 (1.150 to 1.175)	<0.001	<0.001
hsCRP (log-ANCOVA)	Hp+ eradication success vs Hp+ eradication failure	expβ = 0.819 (0.811 to 0.828)	<0.001	<0.001

Adjusted effects were estimated using ANCOVA models specified as: outcome_post ~ outcome_pre + group + age + gender + body mass index + diabetes mellitus + prediabetes + statin use + oral antidiabetic drug use + proton pump inhibitor use + follow-up duration (weeks). Heteroskedasticity-robust HC3 standard errors were applied. For hsCRP, models were fitted on the logarithmic scale and effects are reported as ratios (expβ). The HP− control group served as the reference category. *Holm–Bonferroni adjustment was applied to control the family-wise type I error rate for the two co-primary endpoints (HOMA-IR and hsCRP)*. For abbreviations see Table I.



Fig, 2. Forest plot of adjusted associations for selected metabolic and inflammatory outcomes. Adjusted group effects were derived from ANCOVA-type models adjusting for the corresponding baseline (pre) value, age, gender, body mass index, diabetes mellitus, prediabetes, statin use, oral antidiabetic drug use, proton pump inhibitor use, and follow-up duration (weeks), with HC3 robust standard errors. For skewed outcomes, models were fitted on the logarithmic scale and effects are presented as ratios (expβ). The Hp− control group served as the reference category. Horizontal lines indicate 95% confidence intervals. For abbreviations see Table I.

In the lipid profile, a decrease in triglycerides was observed in the Hp+ eradication success group, while an increase in triglycerides and LDL-cholesterol was observed in the HP+ eradication failure group. Similarly, for inflammation indices (NLR/PLR) and GGT, a pattern associated with lower levels in the Hp+ eradication success group and higher levels in the Hp+ eradication failure group was detected (Table III).

To standardize the follow-up window, analyses limited to 8–12 weeks (n=1901) preserved the co-primary outcomes: for HOMA-IR, Hp+ eradication success vs Hp− control β=−0.111 ($p<0.001$) and Hp+ eradication failure vs Hp− control β=0.395 ($p<0.001$); For hsCRP, Hp+ eradication success vs Hp− control expβ=0.952 ($p<0.001$) and Hp+ eradication failure vs Hp− control expβ=1.167 ($p<0.001$). In the analysis excluding PPI users (n=2,442) and in the reanalysis of non-DM individuals (n=2,659), the HOMA-IR and hsCRP results remained consistent in direction and magnitude.

In addition to the primary ANCOVA approach, the results of the supportive analysis conducted using a difference-in-differences model incorporating group×time interaction were consistent with the main analyses (Table IV). The interaction coefficient for HOMA-IR indicated a lower change pattern in the Hp+ eradication success group compared to the control group; in the Hp+ eradication failure group, it indicated a higher change pattern (Hp+ eradication success: β=−0.115; 95%CI: −0.149 to −0.081; $p<0.001$; Hp+ eradication failure:

Table III. Secondary outcomes (adjusted effects with false discovery rate control)

Outcome	Unit	Model scale	Hp+ success vs Hp− control: effect (95% CI)	p	q value (FDR)	Hp+ failure vs Hp− control: effect (95% CI)	p	q value (FDR)
Fasting glucose	mg/dL	β (units)	-1.208 (-1.707 to -0.708)	<0.001	<0.001	2.839 (2.169 to 3.508)	<0.001	<0.001
Fasting insulin	μIU/mL	Ratio (expβ)	0.978 (0.973 to 0.983)	<0.001	<0.001	1.091 (1.084 to 1.098)	<0.001	<0.001
HbA1c	%	β (units)	-0.025 (-0.034 to -0.016)	<0.001	<0.001	0.081 (0.069 to 0.093)	<0.001	<0.001
Total cholesterol	mg/dL	β (units)	-0.891 (-1.582 to -0.201)	0.011	0.021	0.946 (-0.016 to 1.908)	0.054	0.059
LDL-C	mg/dL	β (units)	-0.781 (-1.418 to -0.143)	0.016	0.026	1.490 (0.638 to 2.341)	<0.001	<0.001
HDL-C	mg/dL	β (units)	0.200 (-0.012 to 0.412)	0.065	0.084	-0.355 (-0.646 to -0.064)	0.017	0.021
Triglycerides	mg/dL	Ratio (expβ)	0.986 (0.980 to 0.991)	<0.001	<0.001	1.060 (1.053 to 1.068)	<0.001	<0.001
Neutrophils	10^3/μL	β (units)	-0.044 (-0.072 to -0.015)	0.003	0.005	0.199 (0.159 to 0.239)	<0.001	<0.001
Lymphocytes	10^3/μL	β (units)	0.013 (0.001 to 0.026)	0.040	0.056	-0.057 (-0.075 to -0.039)	<0.001	<0.001
Platelets	10^3/μL	β (units)	-3.725 (-5.001 to -2.449)	<0.001	<0.001	8.360 (6.609 to 10.111)	<0.001	<0.001
NLR	—	Ratio (expβ)	0.981 (0.970 to 0.992)	0.001	0.003	1.083 (1.067 to 1.100)	<0.001	<0.001
PLR	—	Ratio (expβ)	0.978 (0.969 to 0.987)	<0.001	<0.001	1.064 (1.051 to 1.077)	<0.001	<0.001
AST	U/L	β (units)	-0.210 (-0.483 to 0.063)	0.132	0.153	0.527 (0.140 to 0.915)	0.008	0.010
ALT	U/L	β (units)	-0.666 (-1.068 to -0.263)	0.001	0.003	0.294 (-0.275 to 0.863)	0.311	0.325
GGT	U/L	Ratio (expβ)	0.984 (0.977 to 0.990)	<0.001	<0.001	1.044 (1.035 to 1.053)	<0.001	<0.001
Hemoglobin	g/dL	β (units)	0.030 (0.001 to 0.059)	0.039	0.056	-0.077 (-0.115 to -0.038)	<0.001	<0.001
Albumin	g/dL	β (units)	0.008 (-0.001 to 0.016)	0.069	0.084	-0.038 (-0.049 to -0.026)	<0.001	<0.001
Ferritin	ng/mL	Ratio (expβ)	0.986 (0.980 to 0.992)	<0.001	<0.001	1.035 (1.026 to 1.043)	<0.001	<0.001
Vitamin B12	pg/mL	β (units)	1.620 (-1.188 to 4.429)	0.258	0.284	-8.548 (-12.295 to -4.800)	<0.001	<0.001
25(OH)D vitamin	ng/mL	β (units)	0.345 (0.067 to 0.623)	0.015	0.026	-0.449 (-0.838 to -0.059)	0.024	0.028
Uric acid	mg/dL	β (units)	-0.013 (-0.038 to 0.012)	0.316	0.331	0.055 (0.021 to 0.089)	0.002	0.002
Creatinine	mg/dL	β (units)	0.001 (-0.002 to 0.005)	0.509	0.509	-0.001 (-0.006 to 0.003)	0.565	0.565
TyG (post)	—	β (units)	-0.025 (-0.032 to -0.018)	<0.001	0.002	0.085 (0.075 to 0.095)	<0.001	0.002
FIB-4 (post)	—	β (units)	0.023 (0.003 to 0.044)	0.026	0.039	-0.027 (-0.055 to 0.002)	0.064	0.070

Models were adjusted for the corresponding baseline value (pre), group, age, sex, BMI, diabetes, prediabetes, statin use, oral antidiabetic drug use, PPI use, and follow-up duration (weeks), with HC3 robust standard errors. For skewed outcomes (fasting insulin, triglycerides, NLR, PLR, GGT, ferritin), analyses were performed on the log scale and effects are reported as ratios (expβ). False discovery rate (FDR) was controlled using the Benjamini–Hochberg procedure across the 22 secondary outcomes separately for each contrast (Hp+ success vs Hp− control; Hp+ failure vs Hp− control). For abbreviations see Table I.

β=0.366; 95% CI 0.329 to 0.403; p<0.001). The rate of change for hsCRP was consistent with lower levels in the Hp+ eradication success group and higher levels in the Hp+ eradication failure group (Hp+ eradication success: expβ=0.952; 95%CI: 0.944–0.960; p<0.001; Hp+ eradication failure: expβ=1.163; 95%CI: 1.152–1.175; p<0.001).

DISCUSSION

Our study suggests that *H. pylori* eradication outcome is associated with short-term changes in systemic metabolic and inflammatory biomarkers beyond gastrointestinal symptom management. Compared with H. pylori–negative controls,

Table IV. Controlled pre–post supportive analysis using a difference-in-differences approach (group × time interaction)

Outcome	Comparison	Effect scale	Interaction effect (95% CI)	P value
HOMA-IR	Hp+ success vs Hp− control	Additional change vs control (β)	-0.115 (-0.149 to -0.081)	<0.001
HOMA-IR	Hp+ failure vs Hp− control	Additional change vs control (β)	0.366 (0.329 to 0.403)	<0.001
hsCRP (mg/L)	Hp+ success vs Hp− control	Ratio of change (expβ)	0.952 (0.944 to 0.960)	<0.001
hsCRP (mg/L)	Hp+ failure vs Hp− control	Ratio of change (expβ)	1.163 (1.152 to 1.175)	<0.001

Analyses were conducted on long-format data with two time points (pre and post). Within-subject correlation was accounted for using cluster-robust standard errors at the individual level. Models were adjusted for age, sex, body mass index, diabetes mellitus, prediabetes, statin use, oral antidiabetic drug use, proton pump inhibitor use, and follow-up duration (weeks), including interaction terms with time. For HOMA-IR, the interaction coefficient represents the additional change relative to the Hp− control group. For hsCRP, models were fitted on the logarithmic scale and expβ represents the ratio of change ratios compared with the control group. For abbreviations see Table I.

eradication success showed a more favorable trajectory in insulin resistance and systemic inflammation, reflected by a more favorable trajectory in HOMA-IR and hsCRP, alongside a lower TyG index, whereas persistent infection (eradication failure) showed an opposite or less favorable pattern. Changes in FIB-4 were small but provided additional context on MASLD-related pathways. These contrasting trajectories are compatible with the broader MASLD framework linking metabolic stress to inflammatory biology and with evidence implicating *H. pylori* as a potential contributor to MASLD risk [10–12].

A key strength is the prespecified separation of eradication failure as a distinct comparison group, alongside an *H. pylori*–negative control group. This controlled before–after structure helps distinguish treatment-related changes from time-dependent variation and regression to the mean.

High-sensitivity CRP was a key component of the observed pattern. Meta-analyses suggest CRP may decrease after *H. pylori* eradication [5]. In our study, baseline-adjusted analyses of log-transformed hsCRP showed a less favorable trajectory in persistent infection, consistent with an ongoing infection–related systemic inflammatory tone.

Although evidence on the metabolic axis remains heterogeneous, large-scale studies and recent reviews consistently report an association between *H. pylori* infection and insulin resistance/metabolic impairment [13–15, 21].

Persistent positivity after therapy can be viewed as ongoing exposure, potentially reflecting clustered host-, pathogen-, and treatment-related determinants. However, causal inference is limited by the observational design. In our cohort, statin use was not associated with eradication success, although time-varying medication exposure and adherence could not be fully assessed in this retrospective design. The MASLD inflammation–infection interface is particularly relevant for interpreting our findings. Recent clinical guidance and consensus statements have standardized MASLD nomenclature and management [7, 10, 12], and updated meta-analytic evidence supports an association between *H. pylori* infection and MASLD risk, with increasing emphasis on persistent/active infection states [11, 12, 14]. Our concurrent assessment of liver enzymes (including GGT) together with metabolic and inflammatory markers helps contextualize these patterns across MASLD-related pathways [10–12, 14, 15]. The modest and directionally discordant FIB-4 finding should be interpreted cautiously, as FIB-4 is an indirect surrogate index and may be influenced by small shifts in its component variables over a short follow-up interval. Given the short follow-up interval, this small FIB-4 signal is unlikely to reflect true fibrosis progression and may instead be driven by minor short-term fluctuations in AST, ALT, or platelet count, which are components of the index.

Observational studies of lipid profiles report a significant association between *H. pylori* and dyslipidemia [16]. Large-scale real-world data indicate that the risk of dyslipidemia may increase in the presence of *H. pylori* in diabetic populations [17]. Furthermore, data reporting an increase in the risk of dyslipidemia according to age categories in non-obese and non-diabetic populations suggest that the metabolic effects of infection may not be limited to high-risk subgroups alone [20]. Although lipid changes in our study were modest, their directional consistency across eradication success and failure supports a broader infection-related cardiometabolic pattern [22].

In terms of hematological inflammation indices, a recent study reporting that a high NLR at the time of eradication may be associated with eradication failure supports the idea that the inflammatory background of the eradication failure group may be more pronounced [19]. This is consistent with the hypothesis that the directional divergence observed in indices such as NLR/PLR may reflect differences in systemic inflammatory milieu between eradication success and persistent infection.

Two points are important when assessing clinical significance. Firstly, statistical significance may be easier to achieve in large sample studies; therefore, interpretation should be based not only on p-values but also on effect size, confidence intervals, and biological gradients. Secondly, eradication failure may be a 'risk marker' that could be reflected in clinical outcomes. Therefore, keeping the eradication failure group as a separate comparison arm provides not only methodological but also clinical-interpretative strength.

Several limitations should be acknowledged. Owing to the retrospective observational design, important determinants such as diet, physical activity, weight change, and time-varying medication use could not be captured in a structured manner, leaving room for residual confounding. In addition, the exact timing of PPI discontinuation could not be verified in all cases, introducing potential misclassification. Accordingly, the findings should be interpreted as associations rather than causal effects. In addition, the complete-case approach may have introduced selection bias, as patients with missing paired laboratory data or missing follow-up duration were excluded from the final analysis. Endoscopic and diagnosis-level clinical phenotyping was not available in a sufficiently structured form across the full cohort; therefore, diagnosis-stratified analyses (e.g., peptic ulcer versus gastritis) could not be performed. Finally, the median follow-up was approximately 10 weeks, limiting inference regarding the long-term persistence of the observed biomarker changes.

Clinically, our findings suggest that short-term metabolic changes after treatment are not uniform and depend on the eradication outcome. The observed changes over a median follow-up of approximately 10 weeks were modest and should be interpreted as short-term laboratory shifts rather than long-term metabolic remodeling. Accordingly, our results do not support routine *H. pylori* screening solely for dyslipidemia, nor routine dyslipidemia screening solely on the basis of *H. pylori* positivity. Instead, the findings are hypothesis-generating and support prospective studies with standardized long-term follow-up (e.g., 6–12 months and beyond) to determine whether these changes persist and translate into clinically meaningful risk reduction.

CONCLUSIONS

In this controlled before–after cohort, successful *H. pylori* eradication was associated with a more favorable short-term metabolic and inflammatory biomarker profile than persistent infection or *H. pylori*–negative controls. Exploratory TyG and FIB-4 findings suggested heterogeneous metabolic responses,

while estimated fibrosis-related changes were small. Prospective studies with standardized clinical phenotyping and at least 6–12 months of follow-up are needed to assess durability and clinical relevance before any screening implications are considered.

Conflicts of interest: None to declare.

Authors' contributions: A.Z. conceived the study and designed the methodology. G.A. S.Ö. and S.B. investigated the patients. A.Z. and G.A. collected and analyzed the data. A.Z. drafted the manuscript. All the authors revised the manuscript. A.Z. supervised the study. All the authors read and approved the final version of the manuscript.

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