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Original Article

Causal Relationship between Helicobacter Pylori Antibodies and Immune Thrombocytopenia: A Mendelian Randomization Study

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Abstract. ***Background*: Previous observational studies have suggested a potential causal relationship between Helicobacter pylori (*H. pylori*) infection and immune thrombocytopenia (ITP). However, the evidence for causal inference remains contentious, and the underlying mechanisms require further investigation. To delve deeper into the relationship between *H. pylori* and ITP, we conducted a Mendelian randomization (MR) analysis.**
***Method*: In this study, we used two-sample Mendelian Randomization (MR) to assess the causality of seven different specific protein antibodies targeting *H. pylori* on ITP. 76 single nucleotide polymorphisms (SNPs) related to *H. pylori* antibody levels were obtained from the European Bioinformatics Institute (EBI). Summary data on ITP was obtained from the FinnGen database, and inverse variance weighted (IVW) analysis was identified as our main method. The reliability of the findings was ensured by performing many sensitivity analyses.**
***Result*: Genetically predicted serum levels of *H. pylori* GroEL antibodies were positively associated with an increased risk of ITP (odds ratio [OR] = 1.802, 95% CI 1.106–2.936, *P* = 0.01799). No causal relationship was found between other *H. pylori* antibodies and ITP.**
***Conclusion*: The outcomes derived from our two-sample Mendelian randomization analysis demonstrate a discernible link between the levels of *H. pylori* GroEL antibodies and an augmented susceptibility to ITP. However, it is imperative to expand the sample size further in order to corroborate the correlation between *H. pylori* infection and ITP.**

Keywords: Immune thrombocytopenia; Helicobacter pylori; Mendelian randomization.

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Introduction. Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by isolated thrombocytopenia, ranging from asymptomatic to life-threatening bleeding manifestations, as well as the potential risk of venous thromboembolism.[1] The pathophysiological mechanisms of ITP are exceedingly intricate. Current perspectives suggest that platelets coated with autoantibodies are prematurely destroyed via

Fcγ receptors. Additionally, self-antibodies induce complement-mediated platelet destruction and inhibit megakaryocyte function.[2,3] However, in approximately 50% of patients, platelet antibodies cannot be detected, raising the possibility of alternative mechanisms of platelet destruction. The dysfunctional activity of T cells may perhaps be one of the pathogenic mechanisms underlying ITP.[4] Currently, the treatment of ITP encompasses addressing not only the issue of active bleeding but also includes Glucocorticoids, Thrombopoietin-Receptor Agonists, Immunomodulators, and splenectomy.[1] Furthermore, the the immune thrombocytopenia has been divided in a primary form and secondary forms, among them a few infections play a significant role.[5,6]

Helicobacter pylori infection is a prevalent and typically lifelong condition occurring worldwide.[7] While most infected individuals remain asymptomatic, infection with *H. pylori* is associated with various digestive system disorders, notably peptic ulcers, non-ulcer dyspepsia, and gastric cancer. Furthermore, numerous extraintestinal diseases are also associated with *H. pylori* infection. For instance, its infection shares risk factors similar to those of coronary artery disease.[8] There is also research indicating its association with idiopathic iron deficiency anemia.[9] In the realm of ITP, prior research has indicated that successful treatment of Helicobacter pylori infection can lead to an increase in platelet count, suggesting an association between Helicobacter pylori infection and the onset of ITP. However, the underlying mechanism remains unclear.[10] It is noteworthy that existing studies regarding the causal relationship between ITP and *H. pylori* are all observational, inherently bearing significant limitations. These studies are susceptible to confounding factors, reverse causality, or other biases arising from unmeasured or inaccurately measured variables. The causal relationship between Helicobacter pylori infection and ITP still lacks definitive evidence. Our study is crucial for gaining a clearer understanding of the association between Helicobacter pylori and ITP.

Mendelian randomization (MR) is a robust approach that utilizes one or multiple genetic variants, such as SNPs, to investigate the relationship between exposure and outcome. Through MR, these biases common in observational studies can be mitigated by leveraging genetic variables as proxies for exposure to confirm the causal association of risk factors with the disease.[11] This study employs a two-sample Mendelian randomization analysis to investigate whether current or past *H. pylori* infection increases the risk of developing ITP, providing valuable insights for clinical practice.

Material and Methods.

Mendelian randomization design. A two-sample MR analysis was conducted to evaluate the causality of antibody levels against *H. pylori* on ITP. Three core assumptions are used to determine the genetic instrumental variables (IVs) at the center of the MR analysis (**Figure 1**). Firstly, genetic tools should exhibit a strong correlation with *H. pylori* antibody levels.

Secondly, SNPs should not be associated with confounding factors that could influence the occurrence of ITP and the *H. pylori* antibody. Lastly, IVs should only exert their effects through *H. pylori* antibody levels and not through other pathways.

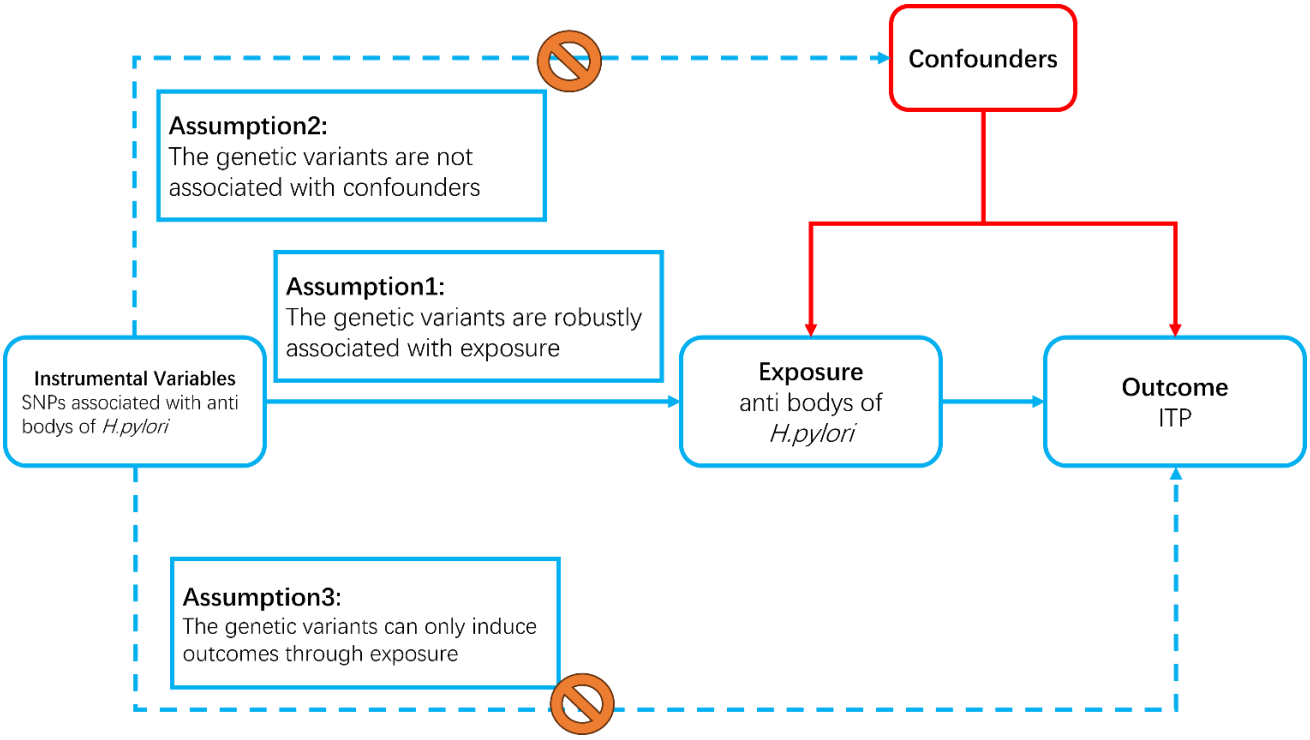

Figure 1. Three core assumptions of the MR analysis.

Data source. The data used for this analysis were sourced from previously published GWAS. *H. pylori* infection was defined based on the measurement of serum-specific antibodies targeting *H. pylori* proteins, incorporating data from seven different antibody measurements. We obtained serum-specific antibody levels for seven *H. pylori* proteins from the IEU OpenGWAS project, namely IgG, CagA, VacA, UREA, OMP, Catalase, and GroEL, including 16,404 European individuals. We sourced the ITP-GWAS summary-level data from the FinnGen consortium's R7 release, which included 605 ITP cases and 304,806 controls.[12] The FinnGen study is a large-scale genomics initiative that has analyzed over 500,000 Finnish biobank samples and correlated genetic variation with health data to understand disease mechanisms and predispositions. The project is a collaboration between research organizations and biobanks within Finland and international industry partners.

Instrument selection. When selecting IVs, as no SNPs met the criteria after setting the p-value threshold to 5 x 10^{-8}, we adjusted it to 5 x 10^{-6}. This threshold has also been utilized in previous MR studies.[13] The linkage disequilibrium (LD) threshold between the SNPs was fixed as $r^2 < 0.001$ (within a window size of 10,000 kb) based on the reference panel data from 1,000 Genomes Project European samples (phase 3) to retain the independent SNPs with the lowest P-values. Then, a sensitivity analysis was conducted to prevent distortion from allele coding or strand orientation, where palindromic SNPs (for example, with G/C or A/T alleles) were taken forward to be ruled out. Weak instrument bias could lead to misleading estimates of causal effects. For missing values, we selected appropriate proxy SNPs from LDlink (https://ldlink.nih.gov/). Additionally, to address potential horizontal pleiotropy and exclude the presence of potential confounders, we assessed the association of IVs with any confounding factors using the GWAS Catalog (ebi.ac.uk). We assessed the strength of instrumental variables (IVs) using the formula $F = \beta^2 exposure / SE^2 exposure$. [14] If the corresponding F-statistic was larger than 10, this indicated sufficient strength to ensure the validity of IVs. Using the aforementioned methods, we successfully identified a total of 76 SNPs.

Statistical analysis. We conducted several analyses based on the two-sample MR framework to investigate the potential causal correlation between *H. pylori* antibody and ITP, including weighted median, MR-Egger regression, inverse-variance weighted (IVW), weighted mode, and simple mode. The IVW approach was used as the primary analysis, assuming that all SNPs were valid but vulnerable to horizontal pleiotropy. The MR-Egger intercept test was employed to identify pleiotropy, where P>0.05 indicates no significant difference, thus suggesting the absence of pleiotropy.

Additionally, sensitivity analyses were conducted, utilizing MR-PRESSO to detect and correct for the impact of outliers in the data. The primary IVW and MR-Egger methods were evaluated for heterogeneity. Cochran's Q-statistic was employed to ascertain whether IVs exhibited heterogeneity, with a P-value > 0.05 indicating there was no heterogeneity. The leave-one-out analysis was employed to ensure that the results remain uninfluenced by individual-biased SNPs. Statistical analyses and data visualizations were performed utilizing R version 4.3.2. Mendelian randomization analyses were performed using the Two Sample MR Package, version 0.6.0.

Figure 2. The result of the MR analysis.

Result. We selected genome-wide significant SNPs with P<5x10^{-6}. Then, we eliminated SNPs in linkage disequilibrium ($r^2 < 0.001$ within a window size of 10,000 kb) and unreconciled palindromic SNPs, leaving us with 76 SNPs of the antibody levels of *H. pylori* IgG, CagA, VacA, UREA, hydrogen peroxide enzyme, OMP, and GroEL. (**Supplementary Table 1**) Subsequent MR-PRESSO analysis confirmed the absence of outliers among these SNPs. After excluding palindromic SNPs, we conducted MR analyses using five methods to assess the relationship between these *H. pylori* antibodies and ITP. The results indicated a significant association

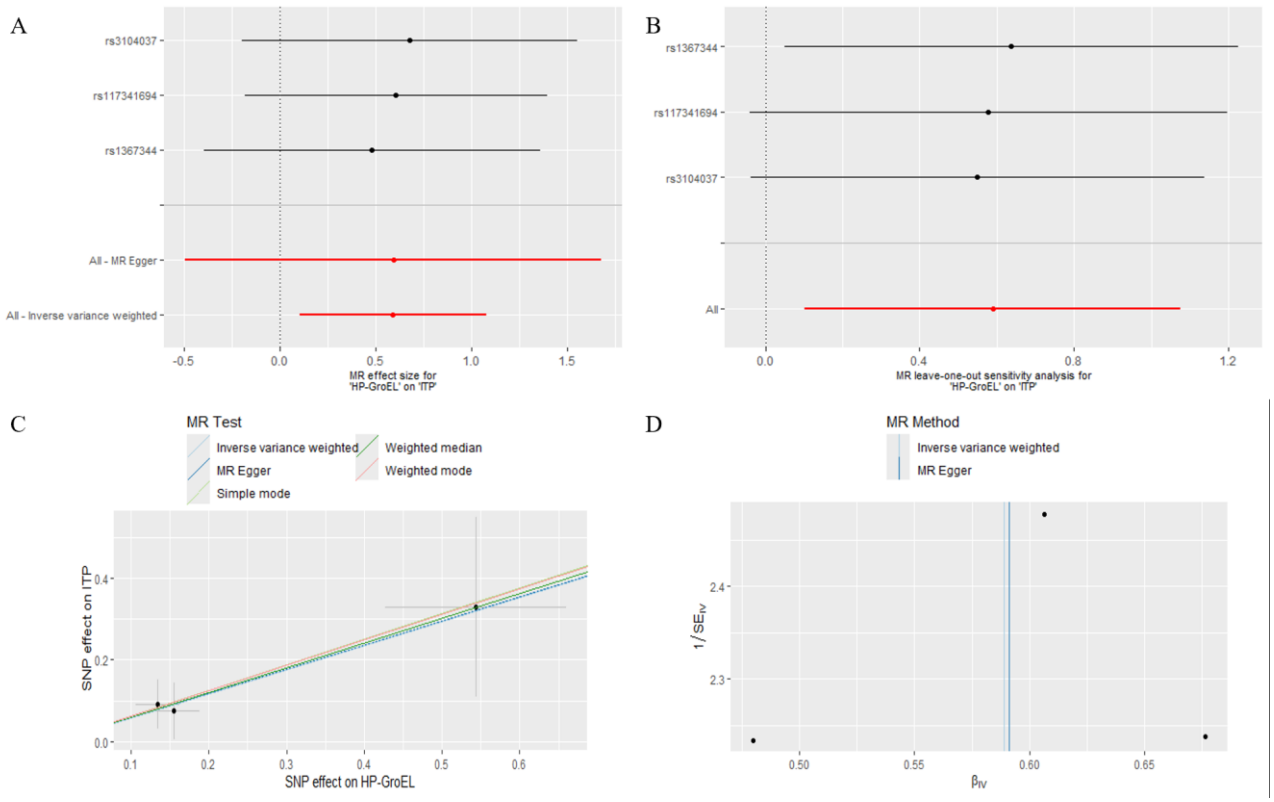

Figure 3. The effect of anti- *H. pylori* GroEL on ITP. (A) Forest plot, (B) Leave-one-out sensitivity analysis, (C) Scatter plot, (D) funnel plot.

between *H. pylori* GroEL antibodies and the risk of ITP under the IVW method. (odds ratio [OR] = 1.802, 95% CI 1.106-2.936, *P* = 0.01799)(**Figures 2 and 3**) To address the issue of horizontal pleiotropy, MR-Egger regression was employed to validate horizontal pleiotropy. The results indicated that all P-values were greater than 0.05, suggesting the absence of horizontal pleiotropy in the instrumental variables (IVs) utilized. In the MR analysis of GroEL, the intercept of MR-Egger was -0.00047 (P=0.9970). The leave-one-out analysis did not reveal any influential IVs affecting the outcomes, suggesting the reliability of the results. Subsequently, the Cochran Q-test was employed to assess the heterogeneity of this study. The results indicated that all P> 0.1, suggesting an overall absence of heterogeneity. Regarding the analysis of GroEL, the Cochran Q-test yielded P-values of 0.75 for MR-Egger and 0.95 for IVW.

Discussion. In 1998, a study from Italy reported that among 11 ITP patients who underwent *H. pylori* eradication, 8 patients experienced a significant increase in platelet count, with autoantibodies against platelets disappearing in 6 of them.[15] In subsequent observational and retrospective studies, approximately 50% of ITP patients with *H. pylori* infection experienced a significant increase in platelet count after eradication of *H. pylori*.[16] In these studies, the response time of platelet count restoration following eradication therapy varies. In one report, platelet recovery was observed as early as 3 days after eradication.[17] Most studies assess platelet count levels starting one month after eradication therapy. While previous observational studies have indeed demonstrated an increase in platelet counts in ITP patients after eradicating *H. pylori*, the precise mechanism remains elusive. Moreover, due to the presence of confounding factors, observational studies carry a degree of uncertainty. MR is founded on the assumption that genetic variations in humans occur at random in the population, are sufficiently independent of confounders, and can be identified as instrumental variables to evaluate the causal relationship between exposure and outcome. In this study, we have uncovered compelling evidence through MR analysis, establishing a definitive causal relationship between *H. pylori* infection and the occurrence of ITP. Among the European population, the antibodies produced due to *H. pylori* infection, specifically GroEL, are directly correlated with the incidence of ITP. In the European population, the production of GroEL antibodies following *H. pylori* infection is directly associated with the occurrence of ITP.

There is considerable research on the mechanism of improving the condition of ITP patients by eradicating *H. pylori*. Some studies suggest that macrolide antibiotics, including clarithromycin (commonly present in eradication regimens), exhibit anti-inflammatory properties. This action could potentially ameliorate platelet autoreactivity in ITP by inhibiting the production of proinflammatory cytokines.[18] Some studies suggest that antibacterial agents used to treat Helicobacter pylori can eradicate symbiotic bacteria responsible for cross-reacting platelet antibodies. However, systematic

reviews have confirmed that the therapeutic effect of eradicating *H. pylori* in ITP is indeed due to bacterial eradication rather than the treatment itself. Actually, platelet reactions are rarely observed in uninfected patients or those with persistent infections.[19]

The GroEL antibody may possess distinct biological effects directly linked to the immune response following H. pylori infection. Studies have indicated that GroEL, as a critical component of H. pylori heat shock proteins, plays a pivotal role in eliciting host immune responses. It is also associated with inflammation and autoimmune reactions, which may have a specific role in the pathogenesis of ITP.[20,21]

Several mechanisms have been proposed to elucidate the connection between *H. pylori* and ITP.

In particular, antibodies against the CagA protein have been shown to cross-react with platelet antigens, resulting in accelerated platelet clearance.[22] The expression of CagA contributes to shifting the Th1/Th2 balance in favor of Th1 by a variety of mechanisms involving induction of lymphocyte cell-cycle arrest, and chronic ITP is also associated with a polarized Th1 type.[23,24] While in our study, the levels of CagA antibodies did not exhibit a strong correlation with ITP, it is noteworthy that the CagA positivity of *H. pylori* varies geographically. For example, in Japan, where both infection rates and response rates to eradication therapy are high, most *H. pylori* strains express CagA, whereas the proportion of CagA-positive strains in Western countries is much lower.[25,26] Moreover, there are structural differences between the Western and East Asian types of CagA. Western strains are characterized by CagA protein, which consists of Glu-Pro-Ile-Tyr-Ala (EPIYA) sites A and B, followed by multiple EPIYA-C.[27] However, Asian *H. pylori* strains are generally characterized by expressing CagA with sites of EPIYA-D.[28] Our study's data is derived from European populations, which may introduce a degree of population bias. For instance, regional variations in *H. pylori* strains and antigen expression could limit the generalizability of the findings to other populations. Moreover, the diagnostic criteria for ITP may vary across different databases. Future research should incorporate data from diverse regions and populations to validate these findings.

Compared to the expensive conventional treatments for ITP, eradicating *H. pylori* is cost-effective and minimally toxic, and its diagnostic methods are non-invasive, making it a treatment worth considering. Particularly in East Asian countries with high treatment response rates, routine screening for *H. pylori* in ITP patients is even more worthy of consideration. Our MR study revealed a significant correlation between GroEL antibodies and the occurrence of ITP in the European population. Subsequent research endeavors will necessitate further investigation on an expanded sample size.

Conclusions. In summary, this Mendelian randomization study highlights a significant causal relationship between H. pylori GroEL antibodies and the risk of developing ITP in a European population. These findings underscore the importance of considering H. pylori eradication as a potential therapeutic strategy for ITP, particularly given the cost-effectiveness and low toxicity of the intervention. However, the study also recognizes the limitations imposed by population-specific factors and the lack of significant associations with other H. pylori antibodies. Future research, to solidify these findings and further explore the underlying mechanisms, should involve larger and more diverse populations investigating the role of different H. pylori strains in ITP pathogenesis. These efforts will contribute to the development of targeted and effective management strategies for patients with ITP.

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Data availability. The present study is based on freely available summary statistics from genome-wide association studies. Data regarding *H. pylori* antibodies are from IEU OpenGWAS (IEU OpenGWAS project (mrcieu.ac.uk)). Summary-level data for ITP can be found at https://finngen.gitbook.io/documentation/

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Authors' contributions. YC made substantial contributions to the conception and design of the work, analyzed the data, and drafted the manuscript. OG and QM made substantial contributions to the design of the study, revised the manuscript, and confirmed the authenticity of all raw data.

Ethics approval. It is not applicable since the study is based on summary-level data. In all original studies, ethical approval and consent to participate were obtained.

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