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Letter to the Editor

Clinical significance of genetic polymorphisms of interleukin-1β and cytochrome P450 2C19 on the eradication of *Helicobacter pylori*

Dear Editor;

Helicobacter pylori (*H. pylori*) *is* a Gram-negative, spiral-shaped and fastidious bacterium that can establish a chronic infection in the human stomach and causes serious digestive diseases e.g. gastric atrophy, peptic ulceration, dysplasia as well as gastric malignancy [1]. Recent reports suggest that *H. pylori* antibiotic resistance, *H. pylori* virulence factors, treatment adhesion, host genetic polymorphisms, nutrition, and lifestyle play a major role in determining *H. pylori* eradication rate [1,2].

Interleukin-1β (IL-1β) is one of the most important members of the inflammatory cytokines produced in response to the presence of *H. pylori* infection. Mucosal IL-1β expression in the stomach not only regulates immune responses to *H. pylori* clearance, but also causes inhibition of gastric-acid secretion [2,3].

Herein, the role of IL-1β polymorphisms in *H. pylori* cure rate was evaluated using a comprehensive statistical analysis. We also determined the combination effect of IL-1β and cytochrome P450 2C19 (CYP2C19) polymorphisms at *H. pylori* eradication rate. We collected all relevant articles that investigated the role of IL-1β polymorphisms in *H. pylori* eradication rate by searching international databases such as ISI web of sciences, PubMed, and Scopus. The search terms used in this process were "*Helicobacter pylori*", "interleukin 1B", "eradication", "polymorphism", "*rs16944*", "*rs1143627*" and "*rs1143634*". Moreover, IL-1β is 100 times more effective than proton pump inhibitors and 6000 times more effective than H2 receptor antagonist (H2RA) in inhibiting gastric acid secretion. The required information such as first author, publish year, location of studies, number of included *H. pylori* infected-cases, therapeutic regimen, type of IL-1β variation, distribution of *H. pylori* cure rate in each variation were extracted in Table 1 [1–5]. The role of IL-1β polymorphisms in *H. pylori* cure rate was determined using odds ratio (OR) corresponding to 95% confidence intervals (95% CI). Heterogeneity in the estimates was determined according to I-squared and Cochrane *Q*-test *p*-value indices and publication bias was determined based on Begg's and Egger's *p*-value test as well as asymmetry of funnel plots.

During the electronic search process, we obtained 512 records. After assessing the title, abstract and full text, finally 5 articles were included in the current analysis. Studies were conducted from 2003 to 2010 in Japan (n = 4), China (n = 1). In eligible studies, data of 1218 *H. pylori* infected-individuals were evaluated. According to the literature, the IL-1β gene in humans has three variations (at position 11511, −31, and +3954 bp). In the included studies, four studies assessed rs16944 polymorphism (IL1β-511), two studies assessed rs1143627 (IL1β-31), and one article assessed the effect of rs1143634 variation (IL1β + 3954) on *H. pylori* eradication rate.

Included studies used various therapeutic regimens such as OAC (omeprazole, amoxicillin, and clarithromycin), LAC (lansoprazole, amoxicillin, and clarithromycin), and RAC (Rabeprazole, amoxicillin, clarithromycin) to eradicate *H. pylori* infection (Table 1).

Our results suggested that *H. pylori* cure rate in individuals harboring the T/T genotype was significantly higher than carries C/C genotype (OR: 1.37; 95% CI: 0.86–2.19; I^2: 29.29%; *p*-value: 0.05). Furthermore, the *H. pylori* eradication rate in the C/T genotype was also significantly higher than the C/C genotype (OR: 1.42; 95% CI: 1.01–1.99; I^2: 22.60%; *p*-value: 0.03).

In the current analysis, we found that the cure rate is significantly higher in individuals who secrete less stomach acid (C/T or T/T) compared to individuals with normal acid secretion (C/C), but no significant difference was observed in eradication rate between individuals with the T/T and C/T genotype. Heterogeneity rate was low in overall estimates and we did not observe any publication bias.

In subgroup analysis, we evaluated the effect of each of rs16944, rs1143627 and rs1143634 polymorphisms on *H. pylori* cure rate separately. Regarding the IL-1β-511 (rs16944), we revealed that the cure rate was significantly higher in individuals harboring the T/T or C/T genotypes than in those with carries C allele.

In addition, we concluded that the cure rate significantly was not differ between individuals harboring the T/T and C/T genotypes. During the analysis of rs1143627 and rs1143634 polymorphisms, we found that T/T and C/T genotypes (genotypes with low gastric acid secretion) have a higher cure rate than C/C genotype (normal gastric acid secretion). The reason for this discrepancy in results might be due to the low sample size and low number of studies. Thus, although the heterogeneity rate in our study was relatively low, we need further large investigations to validate our study findings.

CYP2C19 and IL-1β polymorphisms can independently affect the eradication rate. In this study, we sought to evaluate the additive effect between CYP2C19 and IL-1β variations in *H. pylori* cure rate.

However, our findings revealed a significant combination between CYP2C19 RM and IM genotypes and individuals with carries C/T genotype. According to our analysis, it seems that in both rapid metabolizer genotype and intermediate metabolizer genotype, T allele has a supportive role in reducing gastric acidity, so that the cure rate in RM and IM individuals who carry T allele is significantly higher than IL-1β-511 genotype C/C.

However, funnel plot showed the presence of a significant publication bias in the included studies. In addition, there was considered heterogeneity observed within the overall estimates. In conclusion, IL-1β polymorphisms can meaningfully affect *H. pylori* eradication rate by induction of immune response and affecting the gastric acidity. Evidence suggests that individuals harboring the IL-1β-511 genotype T/T have lower intragastric acidity, more inflammatory cell infiltration, and thus *H. pylori* cure rate, compared with *H. pylori* infected cases carrying C/C

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Table 1
Characteristics of included studies.

First author	Year	Location	No. cases	Regimen	IL-1B variations	Genotype			CYP2C19 genotypes								Ref
						CC	CT	TT	RM			IM			PM		
									CC	CT	TT	CC	CT	TT	CC	CT	TT	
Take	2003	Japan	231	OAC,LAC,RAC	rs16944	47/59	138/172		44/61		12/20	72/92		21/33	22/28		14/15	[1]
Furuta	2004	Japan	336	OAC,LAC	rs16944	75/97	147/164	71/75	17/35	44/56	20/22	49/53	77/82	36/37	9/9	26/26	31/32	[2]
Ishida	2006	Japan	67	LAC	rs1143627	17/40	48/76	22/48	22/43	50/59	27/33	40/46	86/99	26/27	8/8	28/29	14/16	[3]
Sugimoto	2006	Japan	360	OAC,LAC,RAC	rs16944	70/79	164/187	67/76	22/43	50/59	27/33	40/46	86/99	26/27	8/8	28/29	14/26	[4]
Zhang	2010	China	224	OAC,RAC	rs16944	3945	6877	91102	NA	NA	NA	NA	NA	NA	NA	NA	NA	[5]
Zhang	2010	China	224	OAC,RAC	rs1143634	183206	1518	0/0	NA	NA	NA	NA	NA	NA	NA	NA	NA	[5]
Zhang	2010	China	224	OAC,RAC	rs1143627	2224	5762	119138	NA	NA	NA	NA	NA	NA	NA	NA	NA	[5]

genotypes.

We also showed that *H. pylori* eradication rate is significantly higher in individuals who carry T/T and C/T genotypes than in individuals with C/C genotype, but it seems unlikely that there is a significant cure rate in patients with T/T and C/T genotypes. Interestingly, we showed that PM and IM in individuals carrying a T allele decreased intragastric acidity, which led into a significant increase in *H. pylori* cure rate compared with individuals with the C/C genotype. However, low population size and a small number of included studies may lead to inconsistency in the results of the present analysis and previous studies. Moreover, the degree of heterogeneity and the existence of publication bias also indicate the need for further studies to confirm the results of our study.

Ethics approval and consent to participate

Not applicable (this paper was provided based on researching in global databases).

Consent for publish

Not Applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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Authors' contributions

1. MK1 has drafted the work and substantively revised it.
2. YY has drafted the work.
3. MK2 has contributed to design of the work and analysis of data.

All authors read and approved the final manuscript.

Declaration of competing interest

The authors have no conflict of interest.

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