

Effects of *Helicobacter pylori* Eradication on the Platelet Count in Hepatitis C Virus-Infected Patients

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Abstract

Background: *Helicobacter pylori* (*H. pylori*) infection is associated with a low platelet count in patients with immune thrombocytopenic purpura (ITP). While eradication of *H. pylori* is an established therapy for increasing the platelet count in ITP patients, it is unclear whether or not eradication will similarly affect the platelet counts in patients with chronic liver diseases (CLDs). We herein examined the effect of *H. pylori* eradication on the platelet counts in hepatitis C virus (HCV)-related CLD patients.

Methods: A total of 65 patients were enrolled, and the *H. pylori*-positive patients were treated to eradicate *H. pylori*. The eradication of *H. pylori* was assessed using a ¹³C-urea breath test 4 weeks after the completion of the therapy. In addition to the general laboratory variables of HCV-infected patients, including platelet counts, the prothrombin time (PT), and liver function markers (AST, ALT, total bilirubin, alkaline phosphatase, and albumin), we also investigated the presence of splenomegaly via ultrasonography. The platelet counts were measured at 1, 3, and 6 months after the final eradication therapy in order to assess the success of *H. pylori* eradication.

Results: Of the 65 patients with HCV-related CLD, 30 were found to be *H. pylori*-positive. The oral treatment regimen succeeded in eliminating *H. pylori* in 19 patients. These *H. pylori*-eradicated patients included eight males and 11 females, and 15 (78.9%) had liver cirrhosis. Regarding the patients who failed to achieve *H. pylori* eradication, their platelet counts did not markedly differ between pre- and post-treatment. Regarding the patients with *H. pylori* eradication, the platelet counts tended to increase 6 months after the treatment ($9.2 \pm 2.9 \times 10^3/\mu\text{L}$ vs. $10.1 \pm 3.7 \times 10^3/\mu\text{L}$, $P = 0.085$). We also found that the platelet count was significantly increased after the eradication in patients without splenomegaly ($9.8 \pm 2.8 \times 10^3/\mu\text{L}$ vs. $11.0 \pm 3.7 \times 10^3/\mu\text{L}$, $P = 0.040$). Regarding the seven patients whose platelet count in-

creased by more than $20 \times 10^3/\mu\text{L}$ after anti-*H. pylori* treatment, most (6/7, 85.7%) did not have splenomegaly.

Conclusion: *H. pylori* eradication may increase the platelet count in HCV-positive patients, particularly those without splenomegaly.

Keywords: Hepatitis C virus; Chronic liver disease; Thrombocytopenia; *Helicobacter pylori*; Splenomegaly

Introduction

Patients with chronic liver diseases (CLDs) are sometimes required to receive invasive treatments, such as endoscopic therapies for gastroesophageal varices, radiofrequency ablation for hepatocellular carcinoma (HCC), and interventional radiology for portal hypertension. However, thrombocytopenia, a commonly observed complication in patients with CLDs, can be a major problem in relation to such techniques associated with a risk for bleeding [1-3]. In CLD patients, splenomegaly and its associated hypersplenism are generally considered a major cause of thrombocytopenia. However, CLD patients with thrombocytopenia do not always have splenomegaly, and other causes may be involved in the decreased platelet count in such patients.

Helicobacter pylori (*H. pylori*) infection is associated with a low platelet count in patients with immune thrombocytopenic purpura (ITP) [4-8]. While eradication of *H. pylori* is an established therapy for increasing the platelet count in ITP patients, it is unclear whether or not eradication will similarly affect the platelet counts in CLD patients. Since hepatitis C virus (HCV) infection is the most frequent cause for CLD in Japan, we evaluated the effects of *H. pylori* eradication on the platelet counts in HCV-related CLD patients.

Patients and Methods

We prospectively evaluated the effect of *H. pylori* eradication on the platelet count in HCV-related CLD patients. HCV infection was confirmed based on positivity for HCV antibodies and HCV RNA, and patients with the following conditions were excluded from the study: receiving immunosuppressive

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Table 1. Characteristics of the *H. pylori*-Positive Patients (N = 30)

Age (years)	68.8 ± 5.0
Gender (male/female)	16/14
AST (IU/L)	60.5 ± 33.1
ALT (IU/L)	57.8 ± 42.5
γ-GTP (IU/L)	47.0 ± 31.3
ALP (IU/L)	281.5 ± 87.6
Total bilirubin (mg/dL)	0.9 ± 0.3
Albumin (g/dL)	3.8 ± 0.5
Hemoglobin (g/dL)	12.3 ± 1.8
Platelets (× 10 ³ /μL)	98.2 ± 40.9
Prothrombin time (%)	80.9 ± 12.0
HCV genotype (group 1/2)	22/8
HCV RNA (Log copies/mL)	5.6 ± 0.8
Chronic hepatitis/Child-Pugh A cirrhosis/ Child-Pugh B cirrhosis/Child-Pugh C cirrhosis	6/20/4/0

Table 2. Pre-Treatment Characteristics of Patients With Helicobacter pylori Eradication (N = 19)

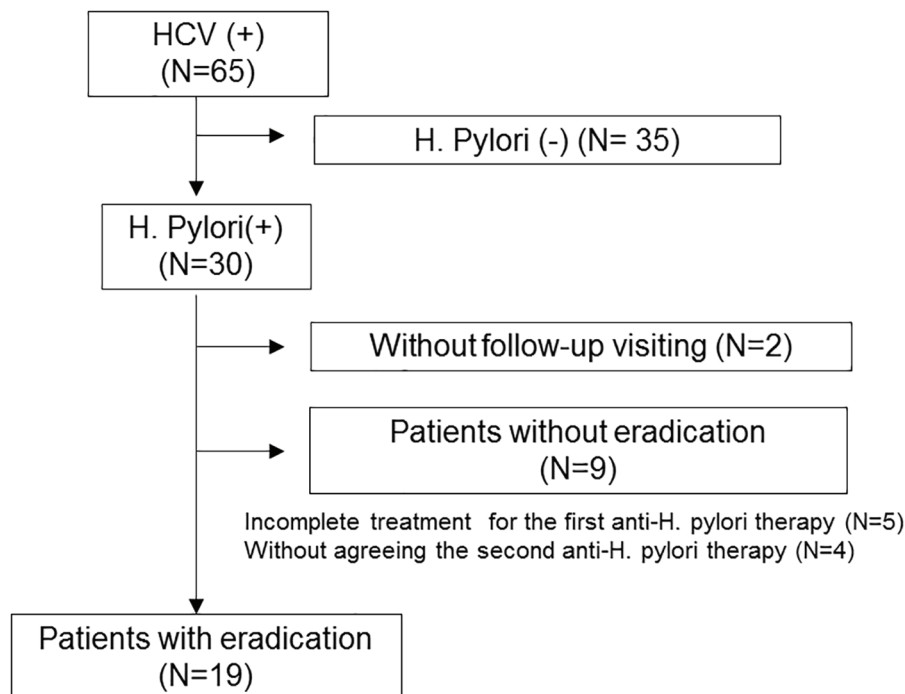
Age (years)	68.1 ± 5.3
Gender (male/female)	8/11
AST (IU/L)	54.6 ± 30.8
ALT (IU/L)	50.8 ± 42.6
γ-GTP (IU/L)	41.4 ± 30.3
ALP (IU/L)	280.9 ± 103.4
Total bilirubin (mg/dL)	1.0 ± 0.3
Albumin (g/dL)	3.8 ± 0.5
Hemoglobin (g/dL)	12.1 ± 1.7
Platelets (× 10 ³ /μL)	91.6 ± 30.2
Prothrombin time (%)	80.8 ± 12.8
HCV genotype (group 1/2)	14/5
HCV RNA (Log copies/mL)	5.7 ± 0.8
Chronic hepatitis/Child-Pugh A cirrhosis/ Child-Pugh B cirrhosis/Child-Pugh C cirrhosis	4/13/2/0

therapy, co-infection with hepatitis B virus, and a history of eradication therapy for *H. pylori*.

We serologically determined the presence of *H. pylori* infection in a total of 65 HCV-infected patients who met the abovementioned criteria, as the measurement of the serum level of *H. pylori*-IgG antibody is considered the most reliable method of confirming *H. pylori* infection in treatment-naive patients in Japan [9, 10]. Then, the *H. pylori*-positive patients

were treated with a standard triple therapy (20 mg b.i.d. omeprazole, 750 mg b.i.d. amoxicillin, and 400 mg b.i.d. clarithromycin) for 1 week. The successful eradication of *H. pylori* was assessed with a ¹³C-urea breath test 4 weeks after the completion of the therapy.

The patients who did not achieve *H. pylori* eradication with the first therapy were subjected to a second therapy (20 mg b.i.d. omeprazole, 750 mg b.i.d. amoxicillin, and 250 mg

**Figure 1.** Algorithm for the classification of HCV-positive patients.

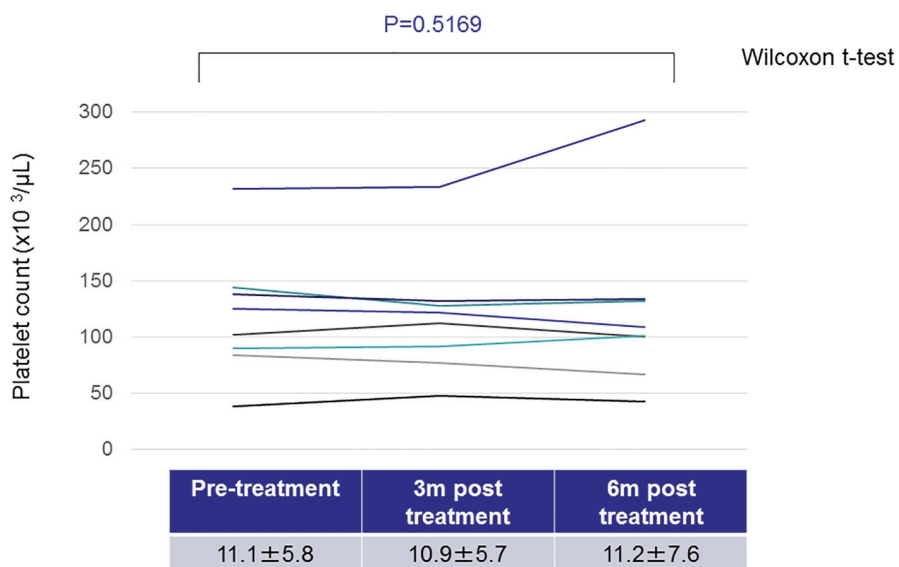


Figure 2. Changes in the platelet counts in patients without Helicobacter pylori eradication.

b.i.d. metronidazole), provided they agreed. The general laboratory variables of HCV-infected patients, including platelet counts, the prothrombin time (PT), and liver function markers (AST, ALT, total bilirubin, alkaline phosphatase, and albumin), were routinely measured. The platelet counts were measured at 1, 3, and 6 months after the final eradication therapy. We also investigated the presence of splenomegaly, via a previously reported method [11].

The numerical variables were expressed as the mean ± standard deviation (SD). The pre- and post-treatment platelet counts were compared using a Wilcoxon *t*-test. A P-value < 0.05 was considered statistically significant.

This study was approved by the Hyogo College of Medicine ethics committee (Approval No. 650) and was conducted according to the Declaration of Helsinki. The current study protocol was registered as a clinical trial (UMIN000002563, <https://upload.umin.ac.jp/>), and written informed consent was obtained from all of the patients.

Results

Baseline characteristics

A total of 65 patients with HCV-related CLD were enrolled in the present study, and 30 were found to be *H. pylori*-positive. The basic characteristics of the *H. pylori*-positive patients are shown in Table 1. The population included 16 male patients and 14 female patients, and the ages of the patients ranged from 56 to 75 years (median 69.5 years). All of the patients had HCV-related CLD, and 24 (80.0%) had liver cirrhosis. In these 24 cirrhotic patients, the Child-Pugh classification was grade A in 20 patients and grade B in four patients. No patients were classified as Child-Pugh C grade.

The oral treatment regimen succeeded in eliminating *H.*

pylori in 19 patients. Of the 11 patients in whom *H. pylori* eradication could not be confirmed, nine actually failed to eradicate *H. pylori*, and two simply missed their follow-up visit (Fig. 1). The basic characteristics of the *H. pylori*-eradicated patients are shown in Table 2. This population included eight male patients and 11 female patients, and 15 (78.9%) had liver cirrhosis. In these 15 cirrhotic patients, the Child-Pugh classification was grade A in 13 patients and grade B in two patients.

Effects of *H. pylori* eradication on the platelet counts in patients with HCV-related CLD

On investigation of the nine patients who did not achieve *H. pylori* eradication, the platelet counts did not change markedly between pre- and post-treatment (Fig. 2). Regarding the 19 patients with *H. pylori* eradication, the platelet counts tended to increase 6 months after the treatment, although the difference before and after treatment did not reach statistical significance (Fig. 3). We found that the platelet counts were significantly increased after the eradication in patients without splenomegaly (Table 3). In addition, regarding the seven patients whose platelet count increased by more than $20 \times 10^3/\mu\text{L}$ after anti-*H. pylori* treatment, most (6/7, 85.7%) did not have splenomegaly.

Discussion

HCV infection is the most frequent cause of CLD in Japan, and a low platelet count in HCV-infected patients can be a major concern when performing certain clinical practices [1-3, 12, 13]. *H. pylori* infection has been reported to decrease the platelet count in ITP patients [4-8]. However, while *H. pylori* infection is highly prevalent in Japan, along with HCV infection,

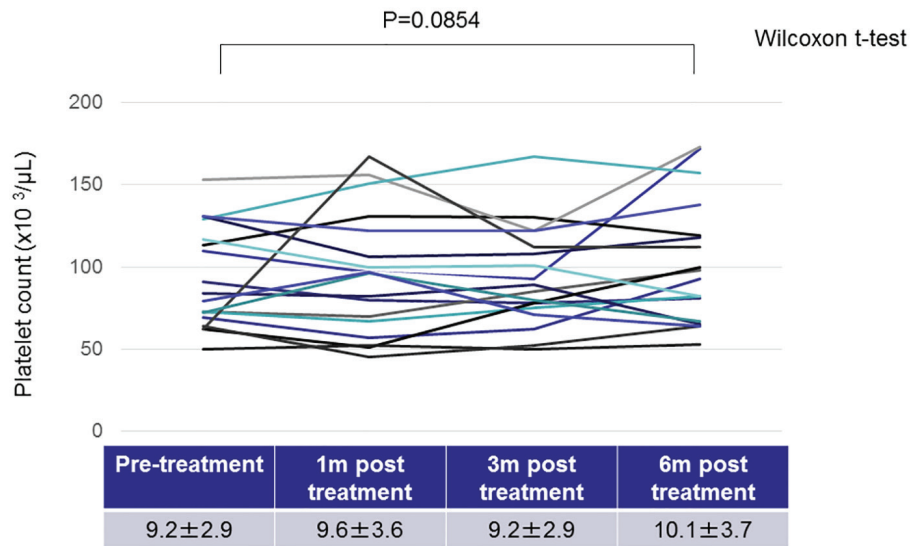


Figure 3. Changes in the platelet counts in patients with Helicobacter pylori eradication.

the association of these two infectious diseases has rarely been studied. We herein examined the effects of *H. pylori* elimination on the platelet count in patients with HCV-related CLD.

The pre- and post-eradication platelet counts in fully *H. pylori*-eradicated patients did not differ significantly. However, in those patients without splenomegaly, the platelet counts significantly increased in response to *H. pylori* eradication (Table 3). These findings suggested that *H. pylori* infection may be related to the decreased platelet count in HCV-related CLD, particularly in patients without splenomegaly.

Recently, oral thrombopoietin receptor agonists such as eltrombopag [14-16] and lusutrombopag [17] have been developed as agents to increase the platelet count. These new drugs reduce the bleeding risk without platelet transfusion under the invasive treatment and have also been reported to be clinically useful. However, eltrombopag administration may

be associated with an increased risk of thromboembolic events in cirrhotic patients, although the precise mechanisms of this event have not been clarified. Therefore, thrombopoietin receptor agonists should be administered only following a careful evaluation of the risks and benefits [14-16]. Since *H. pylori* infection significantly increases the risk of gastric cancer, the Japanese guidelines recommend that all *H. pylori*-infected patients receive anti-*H. pylori* therapy [9]. In the present study, we observed no thromboembolic events; as such, the eradication of *H. pylori* may be a way for HCV-related CLD patients to increase their platelet counts before receiving thrombopoietin agonists.

Several limitations associated with the present study warrant mention. First, we found that the platelet counts were significantly increased after *H. pylori* eradication in patients without splenomegaly. Although these results suggest that *H.*

Table 3. Changes in the Platelet Count Between Pre- and Post-Helicobacter pylori Eradication

Factors	Classification	Platelet count		P-value
		Pre-eradication	Post-eradication	
Age	≥ 70 years (N = 8)	10.3 ± 2.9	11.1 ± 4.4	0.273
	< 70 years (N = 11)	8.2 ± 2.7	9.2 ± 2.6	0.116
Sex	Male (N = 10)	9.6 ± 3.2	11.3 ± 4.4	0.125
	Female (N = 9)	8.9 ± 2.8	9.3 ± 2.9	0.253
Platelet count before treatment	≥ 800 × 10 ³ /μL (N = 10)	8.2 ± 2.7	9.2 ± 2.6	0.116
	< 800 × 10 ³ /μL (N = 9)	7.2 ± 1.2	8.0 ± 1.8	0.188
Splenomegaly	Present (N = 6)	7.9 ± 2.8	8.5 ± 2.7	0.593
	Absent (N = 13)	9.8 ± 2.8	11.0 ± 3.7	0.040
Previous interferon treatment	Present (N = 6)	9.3 ± 2.4	9.5 ± 2.8	0.343
	Absent (N = 13)	9.2 ± 3.2	10.4 ± 4.0	0.081
Hepatocellular carcinoma	Present (N = 11)	8.8 ± 3.3	10.0 ± 4.1	0.137
	Absent (N = 8)	9.7 ± 2.4	10.3 ± 3.1	0.230

pylori infection may be related to the decreased platelet counts in HCV-related CLD patients, we did not clarify the associated mechanism. Second, the effects of *H. pylori* eradication were evaluated in a small number of patients (N = 19), despite the fact that a total of 65 patients were enrolled. Although we were unable to determine the reason for the low rate of *H. pylori* infection, many Japanese patients with HCV-related CLD are elderly and may have severely atrophic gastric mucosa where *H. pylori* cannot thrive. Another study with a larger number of patients will be needed to confirm our results.

In summary, the present findings suggest that *H. pylori* eradication may increase the low platelet count in HCV-positive patients, particularly in those without splenomegaly.

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Conflicts of Interest

The authors declare no conflicts of interest in association with this study.

Abbreviations

CLD: chronic liver disease; HCC: hepatocellular carcinoma; *H. pylori*: *Helicobacter pylori*; ITP: immune thrombocytopenic purpura; HCV: hepatitis C virus; PT: prothrombin time; SD: standard deviation

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