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## EVIDENCE-BASED THERAPY ACCORDING TO THE GUIDELINE FOR GASTRIC ULCERS IS COST-EFFECTIVE IN JAPAN

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*Helicobacter pylori* (*H. pylori*) infection is a major cause of gastric ulcers (GU) and eradication of the infection controls the ulcer with no requirement for maintenance therapy. In Japan, an evidence-based guideline (GL) was first published in 2003 (1<sup>st</sup> version) and then again in 2007 (2<sup>nd</sup> version) with a minor revision under support of the Japanese Ministry of Health, Labor and Welfare (GUGLJ). Adherence to its standards is high, estimated at 80%. GU patients aged 18 or older with active ulcers at the time of diagnosis by an endoscopic examination at National Hospital Organization (NHO) hospitals of Japan were enrolled between September 2004 and April 2005. Subjective and endoscopic outcome, medical treatments and medical costs during the following nine months were analyzed, retrospectively. As a result, 935 patients and 270 doctors in charge from 62 NHO hospitals were analyzed. Among *H. pylori*-positive GU patients, the endoscopic recurrence rate of 24 patients with failure of eradication was 29.2%, which was significantly higher than 8.8% of 194 patients with successful eradication. Successful eradication of *H. pylori* resulted in significantly lower endoscopic recurrence rates for GU patients either with or without administration of non-steroidal anti-inflammatory drugs (NSAID). GUGLJ adherence scores were significantly related to the specialty or knowledge on the GUGLJ of doctors in charge, and the total medical cost consumed. These results suggest that the therapy of GU along with an evidence-based GL is essential to implement cost-effective treatment and the GI experts or the doctors that understand the GUGLJ very well should perform it.

**Key words:** *gastric ulcer, Helicobacter pylori, eradication, guideline, cost effectiveness, non-steroidal anti-inflammatory drugs, histamine H<sub>2</sub> receptor antagonists, proton pump inhibitors*

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### INTRODUCTION

It is well known that *Helicobacter pylori* (*H. pylori*) infection is the major cause of gastric ulcers (GU) and eradication of the infection can reduce the occurrence and recurrence of GU. Many different therapeutic strategies performed might have caused some confusion for therapists, hence causing some disadvantages for cost-effectiveness to public health care. To standardize the therapy for GU patients in Japan, an evidence-based guideline (GL) with the provision of an explanatory flow chart (*Fig. 1*) was first published in 2003 (1<sup>st</sup> version) (1) and then in 2007 (2<sup>nd</sup> version)(2) with a minor revision under the support of the Japanese Ministry of Health, Labor and Welfare (GUGLJ).

It is believed that clinical practice with GLs can improve the quality, appropriateness and cost-effectiveness of health care, and can also serve as valuable education tools. Among 279 GL published from 1985 to 1997, however, the mean adherence to standards by each GL was low, estimated at 43.1% according to the standards for GL development established by Shaneyfelt *et al.* in 1999 (3). On the other hand,

adherence of GUGLJ to these standards is high, estimated at 80% (1). Theoretically, the degree of doctor's knowledge on the GUGLJ and their respective specialties may relate to the degree of their adherence to the GUGLJ for the treatment of the GU patients. A stronger adherence of doctors in charge indicate a stronger adherence to treatment performed for GU patients, which may have resulted in more effective treatment of the GU. Effectiveness means managed and improved control of GU with less expense of the therapy performed. Assessment and eradication of *H. pylori* is important to control gastric cancer development as well, which can follow the *H. pylori* induced chronic gastritis (4). The present study herein has been designed to perform a multihospital analysis to assess the relationship of a doctor's knowledge and specialty for the GUGLJ and the medical cost utilized for the complete treatment of a GU patient, and is referred to as "Japan assessment study on the evidence-based guideline for gastric ulcer with special reference to its outcome: EGGU." To date, no other papers surveying the nationwide cost-effectiveness of GUGLJ-based therapy of GU patients have been published in Japan.

## MATERIALS AND METHODS

*Gastric ulcer patients and doctors in charge*

The present study was a retrospective cohort analysis. GU patients with active ulcers diagnosed by an endoscopic examination between September 2004 and April 2005, and doctors in charge that treated the patients at NHO hospitals were enrolled through an internet registration on the EGGU web site between May 2006 and March 2007. Patients were selected to be  $\geq 20$  years old on April 1, 2006, or  $\geq 18$  years old at the time of GU diagnosed.

Patients were examined for their subjective symptoms relating to the ulcer healing or recurrence when they were enrolled in the present study after the treatment of GU by inquiring about their health conditions *via* mail between May 2006 and March 2007. Health status assessment was performed using SF36, version 2 (5). Those doctors in charge enrolled in the study were surveyed by the EGGU researcher at each hospital by their specialty, whether gastrointestinal (GI) experts, non-GI physicians or other specialists. Their knowledge regarding the GUGLJ was divided into 3 groups based on by the answer to the inquiries about the GUGLJ: knew it very well, just yes or no. Medical records of each patient were examined to discover the endoscopic findings of the ulcer healing or recurrence, and the medical treatments performed. Adherence scores to the GUGLJ were adapted to each category of

performance for the therapy of GU. The total adherence scores were calculated by counting the number of performances and their adherence scores. The present study was undertaken with permission from the ethical committee of the NHO in Japan. All doctors and patients involved with the study had signed their informed consents.

*Flow chart described in the guideline*

Active ulcers are initially checked to determine if they bleed or not. After the bleeding stops or no bleeding is recognized, assessment for non-steroidal anti-inflammatory drugs (NSAID) intake and *H. pylori* infection is undertaken. If *H. pylori* infection is positively identified, and its eradication is performed successfully, no maintenance therapy is requested following the eradication. This flow chart can clearly inform the doctors in charge of the treatment strategy of the GU patient (*Fig. 1*).

*Guideline adherence scores*

In order to calculate the GUGLJ adherence scores, five items shown in *Table 1* were scored. They were 1) NSAID; 2) *H. pylori* infection; 3) ulcer healing treatment; 4) maintenance therapy; and 5) therapy for patients with no *H. pylori* infection. "Comments" in *Table 1* indicated the different activities of the doctors in charge or therapies performed; and "Therapies" indicated the drugs prescribed to the GU patients. For example,

*Table 1.* Guideline adherence scores.

Items	Comments	Therapies	Scores	
NSAID	Presence of medical record describing NSAID intake		5	
	When NSAID intake positive,	Quit NSAID intake	PPI or PG	3
		Continuity NSAID intake	PPI with MP	2
		Continuity NSAID intake	H <sub>2</sub> B and/or MP	1
		Continuity NSAID intake	MP or others	0
	Presence of medical record describing no NSAID intake		5	
No medical records as to NSAID intake		0		
<i>Helicobacter pylori</i> infection	Performance of infection assessment		5	
	No performance of infection assessment		0	
Ulcer healing treatment	When <i>H. pylori</i> infected,	<i>H. pylori</i> eradication performed	5	
		No eradication performed	0	
	After eradication performed,	Assessment performed	3	
		No assessment performed	0	
Maintenance therapy	Performance after eradication,	MTx performed	PPI, H <sub>2</sub> B or MP	1
		No MTx performed		3
	Duration of MTx,	Less than one month	3	
		Between one and three months	2	
		Three months or more	1	
Therapy, with no <i>Helicobacter pylori</i> infection		PPI	3	
		H <sub>2</sub> B, PPI and MP, or H <sub>2</sub> B and MP	2	
		MP	0	
		MP or others	0	

Abbreviations: NSAID, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitors; H<sub>2</sub>B, H<sub>2</sub> blocker (histamine H<sub>2</sub> receptor antagonists); MP, mucosal protectants; MTx, maintenance therapy

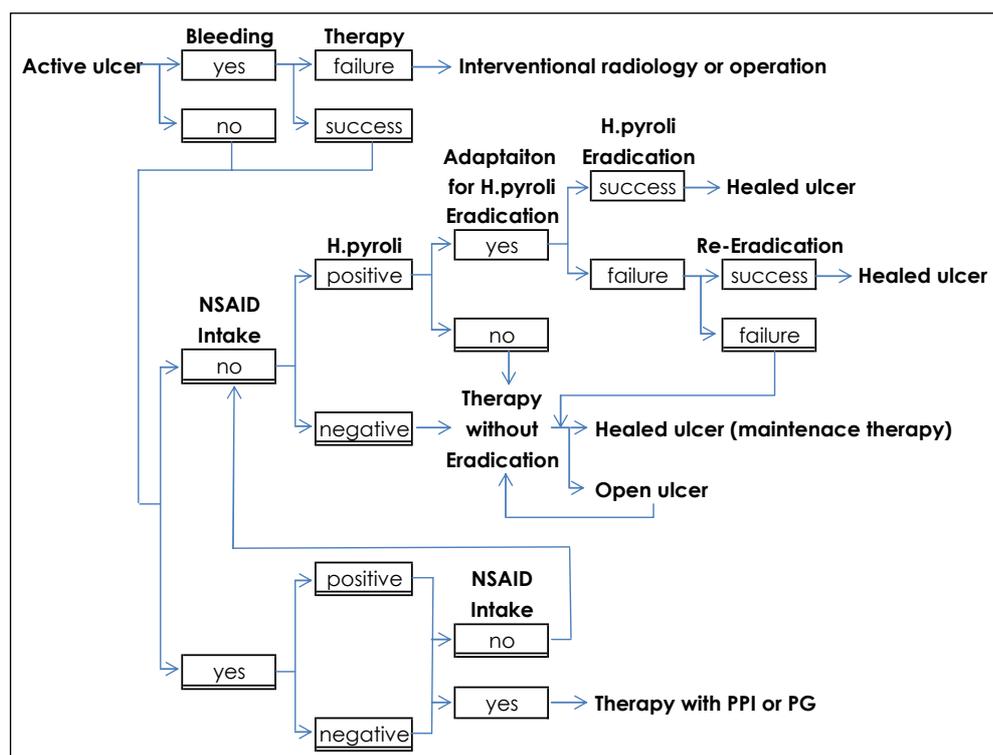


Fig. 1. Flow chart of treatments in the EBM-based Guideline for Gastric Ulcer in Japan.

the presence of description about NSAID intake or the assessment for *H. pylori* infection by the doctor in charge in the medical records was scored 5. On the other hand, no description in the medical records about these two items was scored 0. These scores were determined by the significance for the therapy, which is reflected in the flow chart of the GUGLJ. Finally, the total GUGLJ adherence scores counted were divided into 4 groups: category 1 with a total score of  $\leq 5$ , category 2 with a total score of  $\geq 6$  and  $\leq 12$ , category 3 with a total score of  $\geq 13$  and  $\leq 20$ , and category 4 with a total score of  $\geq 21$ ; the larger category number indicates greater adherence to the GUGLJ. These categories were drawn from the retrospective assessments of the medical record of each GU patient, not from the subjective memory of the doctors in charge. Compliance of the GU patients was not analyzed because it was subjective and difficult to estimate. Subjective data were limited to the health status assessment of GU patients using SF36 version 2. Since the adherence scores and categories were counted utilizing only the objective findings described in the medical record of GU patients, they should be highly reliable.

#### Health status assessment

For the health status assessment of GU patients, SF36 version 2 (5) was applied. This is a program accepted worldwide to assess the health-related quality of life (QOL) of patients. SF36 is a popular tool to compare the patient's physical and mental condition among different diseases. It includes eight subscales: physical functioning (PF), role physical (RP), bodily pain (BP), social functioning (SF), general health perceptions (GH), vitality (VT), role emotional (RE) and mental health (NH), and two summary scores: physical component summary (PCS) and mental component summary (MCS). Letters of inquiry were delivered to each patient and the answers returned to the EGGU office by mail by patient's own voluntary participation.

#### Medical cost utilized for the treatment of gastric ulcer

The relationship between the adherence scores to GUGLJ and the medical cost consumed during the following nine months after the diagnosis of GU was analyzed. All data described in the medical records of GU patients that consulted the NHO hospitals enrolled were analyzed. If the GU patients consulted hospitals other than an NHO hospital, or they consulted the NHO hospitals as result of other conditions, those data were not included in the analysis. When the period of prescription for GU was recorded longer than nine months, the data were excluded from the analysis. Accounting of the medical cost expended was done based on the drugs prescribed, the endoscopic examinations performed, and the medical cost of outpatient clinic and inpatient hospitalization. These accounts were basically done with respect to the National Health Insurance points of Japan. The medical costs of drugs prescribed were accounted for by counting the volume of drugs per day and the duration of drugs prescribed. Generic or non-generic brands of the drugs prescribed were also included in the accounting process. The medical costs of the outpatient clinics were accounted for by counting the number of consultations, and the fees of consultation and prescription with respect to health care insurance. We found that the average duration of hospitalization for GU/duodenal ulcer (DU) was 22.5 days. The National Health Insurance points of GU/DU have been published in the data of the Diagnosis Procedure Combination (DPC) system of the Japanese Ministry of Health, Labor and Welfare. The medical cost consumed for GU/DU therapy in a one-day inpatient hospitalization was accounted for by dividing the National Health Insurance points of GU/DU by 22.5. Then, the total costs of inpatient hospitalization were assessed with that of one-day inpatient hospitalization and the duration of inpatient hospitalization recorded. Finally, the cost of one endoscopic examination, one-day consultation for GU, and one-day inpatient hospitalization for GU were estimated at 11,400; 1,380; and 26,410 Japanese Yen, respectively.

### Statistical analysis

The base-line characteristics of the patients and doctors enrolled were compared by the Student's t-test. Recurrence rates of GU, the medical performances and the GUGLJ adherence scores, the description of whether the patient was a NSAID taker or not, and the assessment of *H. pylori* infection were compared by the chi-square test or Student's t-test. Because the QOL-scores and the medical costs consumed are influenced by gender, age and complications of the GU patients, and whether the patients were NSAID taker or not, the associations between the GUGLJ adherence score and PCS/MCS or the medical cost consumed were investigated by adjusting these factors by a multiple regression analysis using software of JMP8 (SAS Institute Inc., Cary, NC, USA) or STATA11 (StataCorp., Texas, USA), respectively. Different medical costs expended of category 1 to 4 were investigated by the Kruskal-Wallis test. Significance was indicated by a *P* value of less than 0.05.

## RESULTS

### Patients

Initially, 942 GU patients were enrolled but seven patients were dropped out during the follow-up period. Therefore, a total of 935 patients (572 male, 363 female, average age =63.9 years) were enrolled. Out of these GU patients, 283 (30.3%) had a past history of GU and 554 (59.3%) had complications; diabetes in 100, hypertension in 176, heart disease in 107, vascular disease in 107, liver disease in 79 and others in 302. For the GU patients, description whether the patient was an NSAID-taker or not was found in 847 (90.6%) of their medical records, and 162 (17.3%) were NSAID-takers. *H. pylori* infection assessment was performed in 622 (66.5%). Of these GU patients, 75.6% were *H. pylori* positive and 24.4% were negative. Assessment of eradication was performed in 81.3% of *H. pylori*-positive GU patients, and 86.8% of them succeeded in total eradication.

### Doctors in charge of the gastric ulcer patients

In total, 270 doctors (232 male, 38 female, average age =40.9) from 62 NHO hospitals were enrolled. There were 173 (64.1%) GI experts, and 70 (25.9%) non-GI physicians. The doctors in other fields numbered 27 (10.0%). Regarding inquiries about the GUGLJ, 79 (29.3%) doctors in charge answered "yes very well.", 128 (47.4%) answered just "yes." and 63 (23.3%) answered "no."

### Recurrence of gastric ulcer with respect to NSAID status and eradication of *Helicobacter pylori*

NSAID-takers tended to show higher GU recurrence rates than NSAID non-takers, but there was no statistical significance between them (Table 2). On the contrary, the eradication may contribute to the reduction of the GU recurrence in the *H. pylori*-positive GU patients. Among *H. pylori*-positive patients, the GU recurrence rates were significantly lower in patients with successful eradication than those with failure eradication either NSAID takers or not (Table 3).

### Specialty and performance of doctors in charge of the gastric ulcer patients

Table 4 shows that a description of a GU patient being an NSAID-taker or not was related significantly ( $P<0.001$ ) to the specialty of the doctors in charge. On the other hand, the assessment of *H. pylori* infection was carried out most frequently ( $P=0.002$ ) by the doctors in charge who knew the GUGLJ very well. There were no statistically significant relationships between these performances and the GU recurrence (data not shown).

### Therapeutic drugs prescribed

Proton pump inhibitors (PPI) were most frequently prescribed in 30.4% of the 935 GU patients. Among 162 NSAID-takers, 51.2% quitted NSAID intake after the diagnosis of GU. No maintenance therapy was undertaken in 24.4% of 250

Table 2. Relationships among NSAIDs intake and recurrence in the *Helicobacter pylori* negative gastric ulcer patients.

Medication Intake	Number of patients examined	Number of patients with recurrence	
		Endoscopic	Subjective
NSAID -	91	11 (12.1%)	17 (18.7%)
	55	8 (14.5%)	13 (23.6%)
		<i>P</i> =0.669	<i>P</i> =0.473

Abbreviations: NSAID, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitors

Table 3. Relationships among NSAID intake, eradication and recurrence in *Helicobacter pylori* positive gastric ulcer patients.

NSAID Intake	Eradication		Number of patients with recurrence	
	Successful	failure	Endoscopic	Subjective
-	194	0	17 ( 8.8% ) <sup>a</sup>	30 ( 15.5% ) <sup>b</sup>
	0	24	7 ( 29.2% ) <sup>a</sup>	8 ( 33.3% ) <sup>b</sup>
+	24	0	3 ( 12.5% ) <sup>c</sup>	6 ( 25.0% )
	0	6	3 ( 50.0% ) <sup>c</sup>	2 ( 33.3% )

<sup>a</sup>*P*=0.003; <sup>b</sup>*P*=0.03; <sup>c</sup>*P*=0.04

Abbreviations: NSAID, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitors.

*H. pylori*-positive GU patients with successful eradication. Among them, histamine H<sub>2</sub> receptor antagonists (H<sub>2</sub>RA) were prescribed most frequently. On the other hand, among *H. pylori*-positive GU patients with failure eradication and *H. pylori*-positive GU patients with no assessment of the eradication performed, no maintenance therapy was undertaken less frequently, and a PPI was prescribed in double frequency as compared with those for the former 250 GU patients. Among *H. pylori*-negative patients, a PPI was prescribed most frequently (Table 5).

#### Guideline adherence scores

In total, 927 GU patients were analyzed for the GUGLJ adherence scores. The scores showed a significant relationship to the specialty ( $P<0.05$ ), and the knowledge ( $P<0.001$ ) of the doctors in charge (Table 6). There were no statistically significant relationships identified between these categories and the GU recurrence (data not shown).

#### Quality of life of the gastric ulcer patients

To assess the health-related quality of life (QOL) of the GU patients, the SF-36 version 2 was applied. Results indicated that the highest point was scored in the category 4 in all of the subscales (Fig. 2). These subscale scores tended to be higher in male patients, less than 65 of age, no GU recurrence and NSAID non-takers. Then, the relationship between the subscale scores and the GUGLJ adherence scores were examined by a multiple regression analysis with respect to the gender, age and complications of the GU patients, and whether they were NSAID-takers or not. The subscales showed a significant relationship ( $P<0.01$ ) to the PCS, but not to the MCS of SF-36 (data not shown).

#### Direct medical cost expended for the treatment of gastric ulcers

There was a significant difference ( $P<0.001$ ) in the medical cost consumed among the four categories of the adherence to the

GUGLJ scores (Table 7). The total medical cost for these performances in category 4 was calculated as 237,467 Japanese yen, which was 67% of that in category 1, and the least expensive among the four categories with statistical significance ( $P<0.001$ ) (Fig. 3). The complications of the GU patients, whether they were NSAID takers or not, and the GUGLJ adherence score were associated with total medical cost (Table 8).

## DISCUSSION

*H. pylori* is an important factor in the pathogenesis of gastro-intestinal disorders.(6, 7). In the past, *H. pylori* infection has been detected in a range of 56 to 96% of GU patients. This difference may be reflecting the different use of the NSAID among the GU patients (8). In the present study, *H. pylori* infection was detected in 75.6% and NSAID intake was found in 17.3% of GU patients. *H. pylori* and NSAID are known to correlate with the GU recurrence. *H. pylori* infection can increase the risk of GU by an odds ratio of 3.2 (9), and the risk of GU in *H. pylori*-infected NSAID takers was estimated at 61.1 times higher compared with *H. pylori*-negative NSAID non-takers (10). Concerning the use of NSAIDs is the basic issue for GU treatment. The GUGLJ recommends the doctors in charge to perform GU therapy after quitting NSAID intake, if possible. In practice in the present study, 90.6% of GU patients were examined for NSAID intake. The doctors in the other fields than the physicians recorded it less frequently. 51.2% of the NSAID-takers quitted the use of NSAID and 79.0% of them received the PPI treatment. PPI treatment is the first choice for the GU patients with no *H. pylori*-infection or failure eradication, and H<sub>2</sub>RA is the second choice in case of failure eradication according to the GUGLJ. In the present study, PPI and H<sub>2</sub>RA were prescribed most frequently for the GU patients with no *H. pylori*-infection and failure eradication, respectively. *H. pylori* assessment was performed in 66.5% of GU patients. Doctors who knew the GUGLJ very

Table 4. Relationships between specialities of doctors and their performance among 927 patients treated.

Doctor's performance	Number of patients treated by doctors of						
	GI	non-GI	Others		GL Yv	GL Y	GL N
Description as to NSAID intake							
Yes	648 91.0%	133 95.0%	58 77.3%	$P<0.001$	303 93.2%	412 88.2%	124 91.9%
No	64 9.0%	7 5.0%	17 22.7%		22 6.8%	55 11.8%	11 8.1%
<i>H. pylori</i> assessment							
Performed	478 67.1%	85 60.7%	57 76.0%		238 73.2%	305 65.3%	77 57.0%
Not performed	234 32.9%	55 39.3%	18 24.0%		87 26.8%	162 34.7%	58 43.0%
All	712	140	75		325	467	135

Abbreviations: NSAID, non-steroidal anti-inflammatory drugs; H, Helicobacter; GI, gastrointestinal experts; non-GI, non-GI physicians; Does the doctor know about the guideline (GL)? Yv, Yes. I know it very well.; Y, Yes. I know it.; N, No. I do not know it.

Table 5. Therapies for gastric ulcer patients

Patients	Number of patients	Number of patients with					Maintenance Tx Not performed
		NSAID Quit	Drugs				
			PPI	H <sub>2</sub> RA	MP	Others	
All	935		284 30.4%	266 28.4%	186 1.9%	13 1.4%	
NSAID taker	162	83 51.2%	128 79.0%	27 16.7%	58 35.8%	15 9.3%	
<i>H. pylori</i> positive and successful eradication	250		48 19.2%	152 60.8%	69 27.6%		61 24.4%
<i>H. pylori</i> positive but failure eradication	37		14 37.8%	23 62.2%	9 24.3%		5 13.5%
<i>H. pylori</i> positive but no assessment of eradication	53		20 37.7%	24 45.3%	11 20.8%		8 15.1%
<i>H. pylori</i> negative	152		124 81.6%	45 29.6%	59 38.8%	9 5.9%	

Abbreviations: NSAID, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitors; H<sub>2</sub>RA, histamine H<sub>2</sub> receptor antagonists; MP, mucosal protectants; MTx, maintenance therapy

Table 6. Relationships between guideline adherence scores and number of patients treated

Categories	Number of patients treated	Number of patients treated by doctors of							<i>P</i>
		GI	non-GI	Others	GL Yv	GL Y	GL N		
1	266 28.7%	199 27.9%	43 30.7%	24 32.0%	<i>P</i> = 0.047 69 21.2%	145 31.0%	52 38.5%	<0.001	
2	227 24.5%	166 23.3%	43 30.7%	18 24.0%	74 22.8%	122 26.1%	31 23.0%		
3	285 30.7%	217 30.5%	43 30.7%	25 33.3%	107 32.9%	140 30.0%	38 28.1%		
4	149 16.1%	130 18.3%	11 7.9%	8 10.7%	75 23.1%	60 12.8%	14 10.4%		
Total	927	712	140	75	325	467	135		

Abbreviations: GI, gastrointestinal experts; non-GI, non-GI physicians; Av, average of Category 1, Scores ≤5; 2, Scores ≥6 and ≤12; 3, Scores ≥13 and ≤20; 4, Scores ≥21; Does doctor know about the guideline (GL)? Yv, Yes. I know it very well.; Y, Yes. I know it.; N, No. I do not know it.

well did this assessment most frequently. These different specialties or knowledge of doctors in charge may relate to the different GU treatment or the low performance rate of *H.*

*pylori* assessment. In fact, the GI-experts and the doctors in charge that knew the GUGLJ very well treated the most GU patients in category 4.

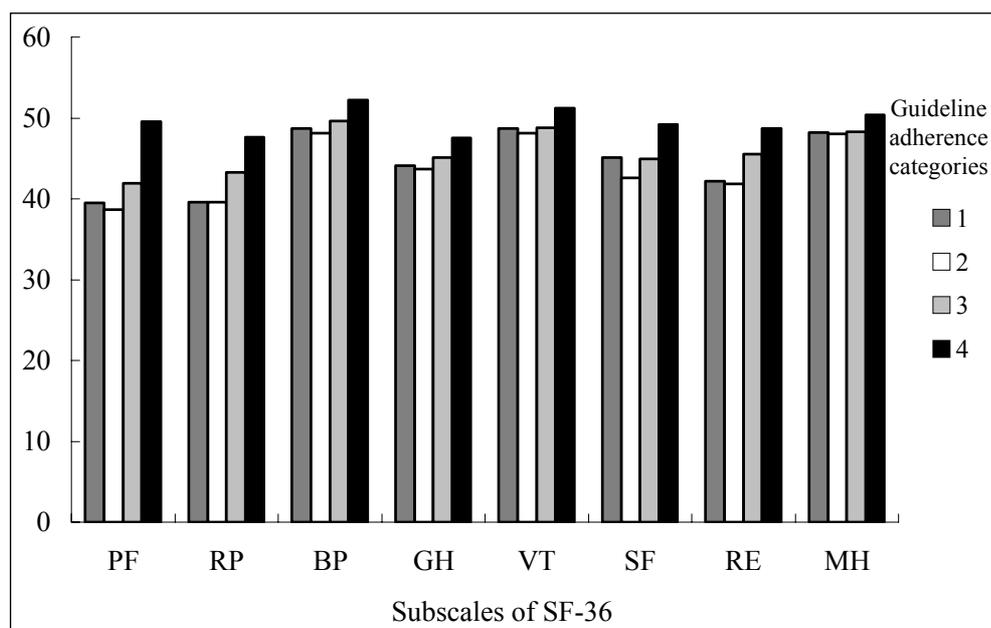


Fig. 2. Guideline adherence scores and the subscales of SF-36. Category 1, Scores  $\leq 5$ ; 2, Scores  $\geq 6$  and  $\leq 12$ ; 3, Scores  $\geq 13$  and  $\leq 20$ ; 4, Scores  $\geq 21$ ; PF, physical functioning; RP, role physical; BP, bodily pain; SF, social functioning; GH, general health perceptions; VT, vitality; RE, role emotional; NH, mental health.

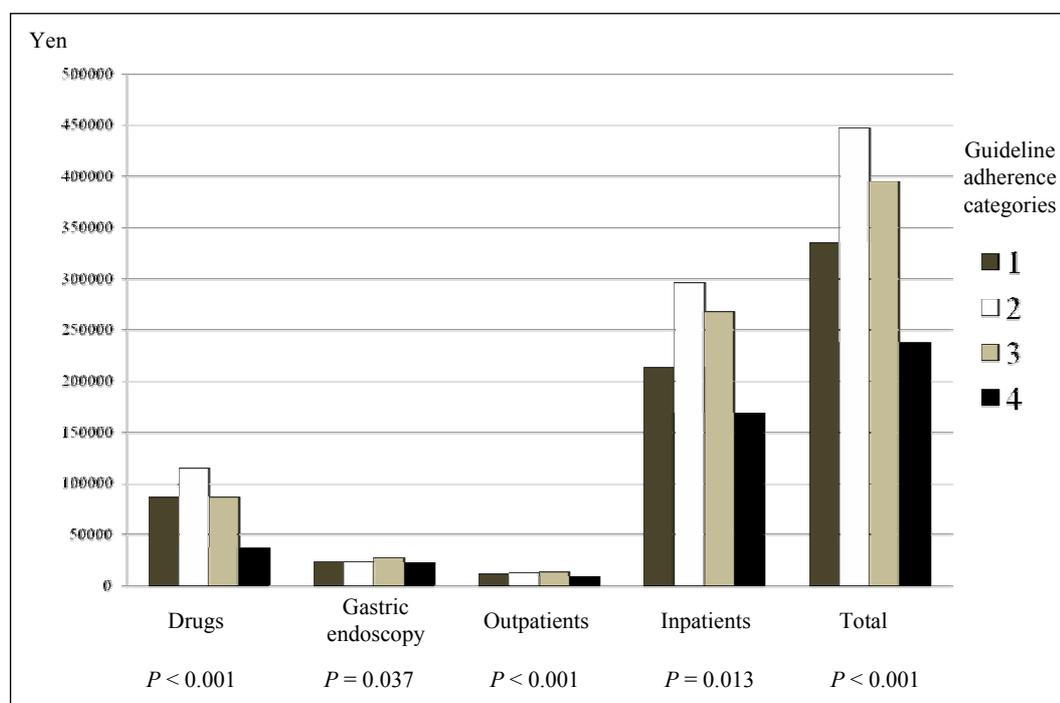


Fig. 3. Guideline adherence scores and the direct medical cost consumed for the GU therapy. Category 1, Scores  $\leq 5$ ; 2, Scores  $\geq 6$  and  $\leq 12$ ; 3, Scores  $\geq 13$  and  $\leq 20$ ; 4, Scores  $\geq 21$ .

Table 7. Relationships between guideline adherence scores and medical costs consumed for treatment of gastric ulcer.

Categories	Number of patients treated	Medical costs consumed for (Japanese Yen)				
		Drugs <sup>a</sup>	Endoscopy <sup>b</sup>	Outpatient <sup>c</sup>	Inpatient <sup>d</sup>	Total <sup>a</sup>
1	266	86,581	23,744	11,619	213,031	334,976
2	227	115,101	23,537	13,101	295,637	447,377
3	285	86,706	27,589	13,296	267,356	394,947
4	149	37,368	22,544	9,042	168,512	237,467

<sup>a</sup> $P < 0.001$ , <sup>b</sup> $P = 0.037$ , <sup>c</sup> $P < 0.001$ , <sup>d</sup> $P = 0.013$ ;

Abbreviations: Category 1, Scores  $\leq 5$ ; 2, Scores  $\geq 6$  and  $\leq 12$ ; 3, Scores  $\geq 13$  and  $\leq 20$ ; 4, Scores  $\geq 21$ ;

In case of no *H. pylori* infection, GU recurred in 12.1% of patients, which was confirmed with an endoscopic examination.

When the failure eradication occurred among the *H. pylori*-positive GU patients, the endoscopic GU recurrence rates

Table 8. Multiple regression analysis for total medical cost expended.

	Coefficient	Standard error	P	95% Confidence interval	
Intercept	10.6	0.225	<0.001	10.1	11
Complication	0.39	0.104	<0.001	0.186	0.595
NSAID takers	0.589	0.143	<0.001	0.309	0.869
Guideline adherence scores					
Category 1	reference		<0.001		
Category 2	0.00127	0.147		-0.287	0.29
Category 3	0.296	0.134		0.0331	0.559
Category 4	-0.402	0.154		-0.704	-0.1

Total medical cost was log transformed.

Adjusted R squared=0.0834

Age and gender were excluded for the final model because of no statistical significance in the multivariate model.

Abbreviations: Category 1, Scores  $\leq 5$ ; 2, Scores  $\geq 6$  and  $\leq 12$ ; 3, Scores  $\geq 13$  and  $\leq 20$ ; 4, Scores  $\geq 21$ ;

increased significantly up to 50% of NSAID-takers and 29.2% of NSAID non-takers. Therefore, the eradication is important to achieve the effective treatment of GU. The GUGLJ recommended several ways of eradication and expected that the successful eradication to be performed. However, it does not exclude the failure eradication itself, since the latter still occurs in substantial numbers even if the ideal eradication has been undertaken. In the present study, no scores were adapted to the failure eradication.

Prescribed aids of GU treatment are to relieve the pain, to promote ulcer healing, and to prevent ulcer recurrence. The eradication therapy could heal GU effectively except for the pain relief and reduce the GU recurrence rate after one year compared to the therapy with acid blockers (11). It was reported that the maintenance therapy with acid blockers and mucosal protectants was insufficient to prevent GU recurrence since 24.6% of GU recurred one year after this combination therapy through the primary care and maintenance therapy of GU in Japan. Labenz *et al.* reported no necessity of the maintenance therapy after the successful eradication of *H. pylori* (12). However, some doctors in charge of GU patients still use acid blockers and mucosal protectants to protect gastric mucosa since chronic gastritis can continue even after the *H. pylori* are eradicated. This maintenance therapy would increase the cost of therapy unnecessarily. In the GUGLJ, the maintenance therapy is recommended to be performed only for the GU patients who are not subjects of eradication therapy. Considering the treatment under the limited budgets of health care insurance, the aspect of cost-effectiveness is an essential issue for the overall treatment. However, in the present study, *H. pylori* infection was assessed for 66.5% of the GU patients, and only 26.7% succeeded in *H. pylori* eradication. Then, only 24.4% had no maintenance therapy following the eradication while 60.8% received H<sub>2</sub>RA. These results may indicate the low coverage of GUGLJ among the doctors in charge for GU patients in Japan during the period of the present study performed. Indeed, there were 712 GI experts but only 325 knew GUGLJ well in the present study.

When estimating the cost-effectiveness of medical treatment, it is important to be clear on what the effectiveness is intended for. Basically, the medical cost expended must include not only the direct performance on the patients but also the indirect performance such as loss of social activity relating to the hospitalization of the patients in the hospital. In the present study, however, the economic estimation could cover the direct

performances for the GU patients who consulted the NHO hospitals on a regular basis and enrolled within the following nine months after the diagnosis of GU. As a result, the different categories of GU therapy could not influence on the GU recurrence, but may influence on the medical cost consumed.

The different medical costs of categories 1 to 4 were attributed mainly to the different cost of drugs prescribed, and the fees of inpatient hospitalization, the latter of which would reflect the duration of hospitalization. As mentioned before, the GU patients in category 4 complained less PCS of QOL than the other GU patients. This would mean those GU patients in category 4 had fewer complications or complaints relating to the shorter time of GU healing, or both. So, it may be possible to consider that they had the least consumption of drugs prescribed, and the smallest fees of the inpatient hospitalization.

GU therapy may be requested if it recurs even five years after the diagnosis of GU. Indirect influence of the GU patients on the economics would vary according to their social activities. In the present study, the adherence scores of the GU patients were not assessed. The medical costs were evaluated by accounting for the direct performance within limited periods. Therefore, the data obtained in the present study could reflect only the adherence of medical professionals, and then some parts of the total cost expended. However, the results obtained in the present study could reflect the practical medicine performed for the GU therapy in Japan, as evaluated from the view points of medical professionals. The present study could conclude that the therapy for GU along with the GUGLJ is essential to perform a cost-effective medicine and it is most effectively performed by the GI experts or the doctors who understand very well the GUGLJ.

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