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Cost Effectiveness Associated with *Helicobacter pylori* Screening and Eradication in Patients Taking Nonsteroidal Anti-Inflammatory Drugs and/or Aspirin

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Background/Aims: This study was performed to investigate the cost effectiveness of *Helicobacter pylori* screening/eradication in South Korean patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and/or aspirin. **Methods:** A decision Markov model was used to estimate the effectiveness and economic impact of an *H. pylori* screening/eradication strategy compared to a no-screening strategy among patients who were included in the model at the age of 40 years. Utility weights were applied to four of the health status groups to reflect quality-adjusted life years (QALY). The costs of screening, *H. pylori* eradication, and managing peptic ulcer and ulcer complications were obtained from South Korea-specific data. **Results:** The total costs per patient were US $2,454 for the *H. pylori* screening/eradication and US $3,182 for the no-screening strategy. The QALYs for the two strategies were 16.05 and 15.73, respectively. The results were robust for the analyses of all different cohort groups who entered the model at the age of 30, 50, or 60 years and for NSAIDs-naïve patients. Through the probabilistic sensitivity analysis, the robustness of our study's results was also determined. **Conclusions:** The *H. pylori* screening/eradication strategy was found to be less expensive and more effective compared to the no-screening strategy among South Korean patients taking NSAIDs and/or aspirin. **(Gut Liver 2013;7:182-189)**

Key Words: Cost-benefit analysis; *Helicobacter pylori*; Mass screening

INTRODUCTION

The prevalence of *Helicobacter pylori* infection was reported to be higher in developing countries than developed countries.[1] With economic developments, the prevalence of *H. pylori* in South Korea has decreased but still remains higher than that of Western societies. In 1998, 66.8% of individuals without a history of *H. pylori* eradication had a positive serology test results; this declined to 59.6% in 2005.[2]

A recent systematic review reported that the annual incidence of peptic ulcer disease (PUD) in Western countries is 0.10% to 0.19% for physician-diagnosed PUD cases and 0.03% to 0.17% based on hospitalization.[3] Over time, the incidence or prevalence of PUD has slightly decreased, which may have been caused by decreased rates of *H. pylori* infection.[3] There have been few data for the prevalence of PUD among Asians, which might be different among Asians. In South Korea, the prevalence of PUD has not decreased although the prevalence of *H. pylori* infection has declined.[4] This may have been caused by the increasing use of nonsteroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin due to the rapidly increased elderly population. In particular, patients treated with NSAIDs and aspirin have a higher risk of developing severe ulcer complications without any symptomatic signs due to the analgesic effects of these drugs.

Eradication of *H. pylori* is generally regarded as a cost-

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effective method for preventing PUD associated with NSAIDs treatments in Western countries. National Institute for Health and Clinical Excellence (NICE) compared several strategies (i.e., do nothing, *H. pylori* eradication alone, treatment with proton pump inhibitor [PPI], administration of misoprostol, *H. pylori* eradication followed by misoprostol treatment, or *H. pylori* eradication followed by PPI treatment) as a prophylaxis against peptic ulcer bleeding in NSAIDs users.[5] This group concluded that two strategies including '*H. pylori* eradication alone' and '*H. pylori* eradication followed by misoprostol if not tolerated, otherwise switching to PPI' were the most cost-effective.[5]

There are other reasons for the preference of *H. pylori* eradication over antisecretory treatment. First, antisecretory treatments require long-term compliance. Second, the cost of long-term treatment with antisecretory agents is overpriced. Guidelines by American College of Gastroenterology recommended *H. pylori* screening and treatment with *H. pylori* eradication therapy for patients who need long-term NSAIDs therapy regardless of the associated risk factors.[6,7] However, in Asian countries like South Korea, which have a higher prevalence of *H. pylori* infection, there is controversy over the universal application for the screening/eradication of *H. pylori* infection. The guidelines by Korean Association of Gastroenterology have mentioned long-term NSAIDs users as one of possible indications for the screening/eradication of *H. pylori*.[8] However, they are not covered by national insurance.[9]

Based on this background, the aim of the present study was to evaluate the cost-effectiveness of *H. pylori* screening/eradication for NSAIDs or aspirin users in South Korea, which has a high prevalence of *H. pylori*.

MATERIALS AND METHODS

1. Decision analytic model overview

A combined decision tree and Markov process model were used to estimate the effectiveness and economic impact of a *H. pylori* screening/eradication strategy compared to a no-screening strategy among patients who required treatment with NSAIDs or aspirin. This model assumed that all patients were screened and *H. pylori* infection was eradicated if they were positive for *H. pylori* in *H. pylori* screening/eradication strategy. Patients treated by the no-screening strategy were neither screened nor treated for *H. pylori* infection.

For the base model, patients entered the model at the age of 40 years old. The 3-month long cycle reflected disease processes such as treatment or exacerbation. Patients in this model died based on the death transition probability due to ulcer complication or natural causes depending on age-stratified life expectancy. It was assumed that all of these individuals died before the age of 100 years.

There were five possible health statuses into which a patient could transit: well, ulcer, ulcer complication (bleeding), death

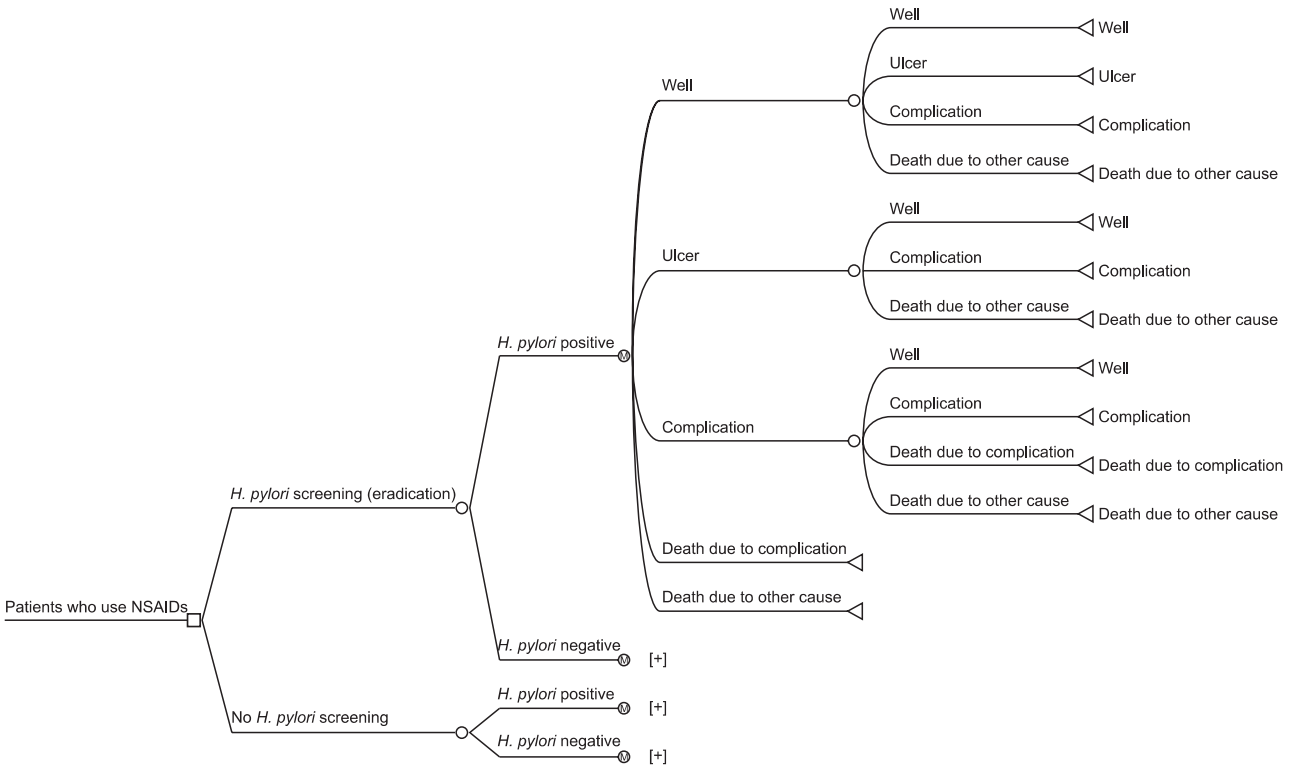

Fig. 1. Decision analytic model for *Helicobacter pylori* screening/eradication versus no-*H. pylori* screening.
NSAIDs, nonsteroidal anti-inflammatory drugs.

due to bleeding, and death due to other cause.

The definitions of ulcer, ulcer complication, death due to bleeding, death due to other cause were as follows: Well is no gastric intestinal symptoms in addition to no endoscopic lesion required treatments; Ulcer is defined endoscopical ulcer of which diameter at least 5 mm which needs treatments; Ulcer complication is defined as perforated and bleeding peptic ulcers; Death due to bleeding is mortality due to ulcer complication; Death due to other cause means natural death due to other causes than ulcer complication.

The probability of disease transition for each health status was obtained from the literature.[10-12] For the present study, values for all causes of mortality rate were obtained through the Complete Life Table published in 2009 by the South Korean Statistical Office,[13] and values for death rate due to complication were derived from published data sources.[11] Transition into the next health status depended on the current health status. This model was established after several meetings with clinicians and methodologists to reflect real-world situations. The basic model is described in Fig. 1. The conceptual framework for this Markov process model was similar to that of a previous study.[5]

2. Epidemiology data

We used South Korean-specific *H. pylori* prevalence data.[2] This data was collected from a total of 7,792 adults (≥30 years old) who visited hospitals located in all parts of South Korea for medical check-ups and had no history of *H. pylori* eradication.[2] Overall seropositivity rates for *H. pylori* were within a range of 50% to 65% depending on patient age. As shown in Table 1, the per-protocol eradication rate of PPI-based triple therapy was assumed to be 80% in South Korea.[14]

3. Effectiveness of *H. pylori* eradication to prevent development of PUD

Since South Korean data for the transition probability for PUD development and complications when comparing *H. pylori* eradication to none among NSAIDs or aspirin users were not available we obtained from a literature review. Based on the Vergara *et al*.'s meta-analysis regarding the probability of transition to ulcers and complications among individuals taking NSAIDs were used.[10] The development rate of PUD was 7.4% and 13.3% for the *H. pylori* eradication and noneradication groups, respectively, among NSAIDs users. If the data were restricted to the NSAIDs-naïve patients, the difference for PUD development was significantly greater. That is, 13.7% of the patients in the noneradicated group had PUD while 3.8% of the patients in the eradicated group developed this disease. This meta-analysis result was almost similar to the NICE health technology assessments published in 2007.[5]

4. Quality of life

Utility weights were applied to five health statuses (i.e., well, ulcer, complication, death due to complication, and death due to other cause) in this model to reflect quality adjusted life year (QALY). Since utility weight worsens with aging, participants designated with "well" and "ulcer" status had the utility weights depending on their age. Specific utility weights for applicable ages were obtained using the 2007 to 2009 Korean National Health and Nutritional Examination Survey Data, which was a national survey representative of the South Korean population.[15] For example, the utility weights for the "well" and "ulcer" status at 40 years of age were 0.931 and 0.889, respectively, using the same database.[15] The utility weights of complication during the initial 3 months of "bleeding" status was 0.460 based on a previous report.[16] Death was valued as zero regardless of the cause (Table 1).

5. Medical costs

The screening/eradication strategy was associated with screening and eradication costs; the no-screening strategy was not. Costs for the screening strategy were determined by multiplying each health examinations by unit costs. Screening costs included costs for physician visits, endoscopic examination, and biopsy for the *H. pylori* test, and *Campylobacter* like organism tests. Eradication costs included ones for medical therapy with PPI-based triple therapy.[17] This regimen included the standard therapy such as b.i.d. for PPI, 1 g b.i.d. amoxocillin, and 0.5 g b.i.d. clarythromycin for 1 week. The costs for these medications were calculated using weighted average costs.[18] Eradication therapy was assumed to be administered only once when patients had positive *H. pylori* screening results. The positive rate for *H. pylori* screening was assumed to be 60% based on South Korean-specific *H. pylori* prevalence data.[2]

Patients with a "well" status had no associated costs because they did not have any clinical symptoms. Costs for treating ulcers with bleeding or without bleeding were drawn from a previous report,[19] In this South Korean report, the annual cost for treating ulcers without bleeding was around US $930 (benign gastric ulcers, US $959.6; duodenal ulcer, US $901.4). When bleeding occurred due to PUD then the cost increased 2.6 times compared to ulcers without bleeding (benign gastric ulcers, US $2,553.1; duodenal ulcers, US $2,316.4).[19] These costs were divided by four before being entered into the model to account for the periods for each cycle. Costs for death were entered as zero (Table 1). All costs are adjusted for 2011 currency values.

6. Statistical analysis

In the base model, the cost-effectiveness of the *H. pylori* screening/eradication strategy was compared to the no-screening strategy based on the outcomes (i.e., incurred costs and gained QALY) observed when the cohort patients were 40 years old. Aside from the base model analysis using data which was collected starting at the age of 40 years old, a different cohort group (i.e., patients who entered the model at the age of 30, 50,

Table 1. Model Input Parameters

Parameter	Base case value	Ranges for sensitivity analysis	Reference
H. pylori-positive prevalence under no-screening/eradication (prevalence considering eradication rate of 80%), yr*			
30-39	49.7 (9.9)	37.3-62.1 (7.4-12.4)	2, 14
40-49	60.6 (12.1)	45.5-75.8 (9.1-15.1)	
50-59	64.8 (13.0)	48.6-81.0 (9.8-16.3)	
60-69	64.7 (12.9)	48.5-80.9 (9.7-16.1)	
70-79	60.7 (12.1)	45.5-75.9 (9.1-15.1)	
Transition probability			
H. pylori-positive/no eradication			
Well to ulcer	13.3	12.0-14.0	10
Well to complication	1.2	1.1-1.3	
H. pylori-negative/eradication			
Well to ulcer	7.4	6.8-8.0	
Well to complication	0.0	-	
H. pylori-positive/-negative			
Ulcer to complication	30.0	25.0-35.0	12
Complication to complication	10.0	8.4-19.4	11
Complication to death due to complication	2.0	1.4-5.8	
Death due to other cause, yr			
30-39	0.00092058	-	13
40-49	0.00206287	-	
50-59	0.00432064	-	
60-69	0.00996799	-	
70-79	0.02728096	-	
More than 80	0.08971054	-	
Utility weight			
Well, yr			
30-39	0.937	0.932-0.941	15
40-49	0.931	0.927-0.934	
50-59	0.903	0.897-0.910	
More than 60	0.824	0.816-0.832	
Ulcers, yr			
30-39	0.881	0.690-1.072	16
40-49	0.889	0.862-0.917	
50-59	0.806	0.738-0.874	
More than 60	0.720	0.661-0.779	
Complication	0.460	0.370-0.560	
Death due to complication	0	-	
Death due to other cause	0	-	
Annual costs*, US $			
H. pylori screening/eradication	130	98-163	17, 18
Ulcer	930	495-825	19
Complication	2,400	1,624-2,706	

Data are presented as percentage or transition probabilities.
*SD was calculated using the mean value of ±25%.

or 60 years) was analyzed. In addition, a cohort of patients who were NSAIDs-naïve and 40 years old was analyzed.

To evaluate the impact of the uncertainty of input data, probabilistic sensitivity analysis with 10,000 simulations was carried out. Costs and disease transition probabilities were assumed to have a gamma distribution while utility weights were assumed to have a triangular distribution. From the applicable distribution for cost, transition probability, and utility weight, one random value was drawn, and then incremental cost and QALY were calculated. If the process is repeated 10,000 times, 10,000 plot values are drawn in the plane of the incremental cost and QALY. Using this scatter plot, we could determine whether the study results were robust or not. A discount rate of 3% was applied to both the effectiveness and cost. TreeAge 2009 (TreeAge Software Inc., Williamstown, MA, USA) and Microsoft Excel 2007 (Microsoft Corp., Redmond, CA, USA) were used for these analyses.

RESULTS

1. Base case analysis

Total costs per patient for *H. pylori* screening/eradication was US $2,454 and that for the no-screening strategy was and US $3,182. QALYs for the two strategies were 16.05 and 15.73, respectively. The *H. pylori* screening/eradication strategy was less expensive (US $728 in cost saving) and more effective (QALY gain of 0.32) compared to the no-screening strategy (Table 2).

Results of different cohort group analysis for participants aged 30, 50, and 60 years old were similar to those of base analysis. The *H. pylori* screening/eradication strategy was dominant for all cohorts. In addition, the *H. pylori* screening/eradication strategy was more cost effective among the younger cohorts. For the cohorts who entered the model at the ages of 30, 40 (base case), 50, and 60 years, QALY gains were 0.43, 0.32, 0.22, and 0.13, respectively, and the cost savings were US $863, US $728, US $568, and US $389, respectively. Furthermore, the subgroup of NASIDs-naïve patients had the greater QALY gains (0.47) and cost savings (US $1,234), when compared to the base case or other subgroups.

2. Sensitivity analysis

The probabilistic sensitivity analysis with 10,000 simulations showed that incremental QALYs (i.e., QALYs for the *H. pylori* screening/eradication strategy minus QALYs for the no-screening strategy) were positive for 95% or more cases, and incremental cost values of 95% or more cases were negative. In addition, a scatterplot was drawn (Fig. 2). In this plot, most dots were located in the area representing positive value for incremental effectiveness (i.e., higher QALY) and negative value for incremental cost (i.e., lower costs) compared to no-screening strategy. These findings indicate the robustness of our study results.

Table 2. Base Case Analysis and Sensitivity Analysis According to Cohort Starting Age and NSAIDs Naïve-Patients

Strategy	Costs, US $	Incremental costs, US $	Effectiveness, QALY	Incremental effectiveness, QALY	ICER, US $/QALY
Base case analysis (40 yr old)					
H. pylori screening/eradication	2,454	-728	16.05	0.32	(Dominate)
No *H. pylori* screening	3,182		15.73		
Model for patients who entered the model at the age of					
30 yr					
H. pylori screening/eradication	2,846	-863	19.11	0.43	(Dominate)
No *H. pylori* screening	3,709		18.68		
50 yr					
H. pylori screening/eradication	2,000	-568	12.46	0.22	(Dominate)
No *H. pylori* screening	2,568		12.24		
60 yr					
H. pylori screening/eradication	1,507	-389	8.70	0.13	(Dominate)
No *H. pylori* screening	1,896		8.57		
Or NSAIDs naïve individuals					
H. pylori screening/eradication	1,614	-1,234	16.30	0.47	(Dominate)
No *H. pylori* screening	2,848		15.83		

NSAIDs, nonsteroidal anti-inflammatory drugs; QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

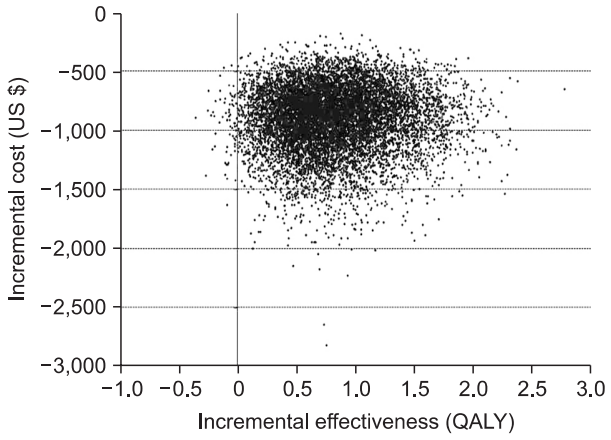

Fig. 2. Incremental cost effectiveness scatterplot for the base model. For probabilistic sensitivity analysis with 10,000 simulations, a scatterplot was created. In this scatter plot, most dots were located in the area representing positive values of the incremental effectiveness (i.e., quality adjusted life years [QALY] gain) and negative values of incremental cost (i.e., cost saving). Incremental effectiveness was calculated by subtracting the QALY of the no-*Helicobacter pylori* screening from the QALY of the *H. pylori* screening/eradication. In addition, incremental cost was calculated by subtracting the costs of the no-*H. pylori* screening from the costs of the *H. pylori* screening/eradication.

DISCUSSION

In the present study, a *H. pylori* screening/eradication strategy was found to be less expensive and more effective compared to a no-screening strategy in South Korea, an area where *H. pylori* is endemic. Based on the different cohort group analysis results (i.e., for patients who entered the model at the age of 30, 40, 50, or 60 years), the *H. pylori* screening/eradication strategy was more cost-effective for the younger cohort than the older cohort. This result was consistent with those of previous economic analyses for *H. pylori* screening/eradication in patients treated with NSAIDs in Western countries.[5] Health technology assessments by NICE also showed that *H. pylori* screening/eradication is the most cost-effective strategy.[5] This report found that, *H. pylori* screening/eradication strategy has a QALY was more than 0.18 QALY and incremental costs was £235 less, compared to the do nothing.[5] Interestingly, these numbers are similar to those from our study (i.e., a QALY gain of 0.32 and cost saving of US $728).

In a randomized study performed in China with a sample size of 100 patients, showed that, *H. pylori* screening/eradication prior to initiation of NSAIDs treatments reduced ulcer formation rates and mean direct medical costs compared to a noeradication strategy.[20] However, one article from the United States reported substantial incremental costs of US $16,805 and US $31,842 to prevent symptomatic ulcer and complicated ulcer respectively, with a *H. pylori* screening/eradication strategy compared to a no-screening strategy.[21] This study demonstrated the benefit of *H. pylori* screening/eradication for the prevention of ulcers similar to our study. However, *H. pylori* screening/eradication was not beneficial in terms of cost, which is different from the conclusions based on the present study. That is, this study raised question regarding whether effectiveness outweighs costs.[21] The authors also suggested that *H. pylori* screening/eradication may be cost-effective if the risk of ulcers due to *H. pylori* infection was assumed to be higher. Several reasons might explain the difference between these two studies. First, the assumed ulcer development rates were different. This study applied 2.1% versus 1.4% ulcer development rates among NSAIDs users depending on the status of *H. pylori* positive and negative,[21] but our study used 13.3% versus 7.4% ulcer development rates, respectively. The difference of ulcer development rates between two studies may be due to ethnicity and regional difference as indicated in previous studies.[22-24] Generally, Asian countries have higher PUD prevalence than Western countries, which is seemed to be contributed by the differences of the prevalence of *H. pylori* between two areas. Higher prevalence of *H. pylori* in Asian countries is seemed to be caused by the environmental sanitization, especially clean water. Cultural practice may be another reason. In Asian countries, close maternal contact to children such as sharing the same bed and eating with sharing the bowel would increase mother-to-child transmission of *H. pylori* and passing the grass around when people drink together may also increase the infection of *H. pylori*. In addition, differences on diet and genetics seem to be the risk factors for greater prevalence of *H. pylori* infection in Asians.[22]

Second, the *H. pylori* infection prevalence and medical costs reported by the two studies were different. It is already known that cost-effectiveness analysis is affected by disease epidemiology, availability of healthcare resources, variation in clinical practice, and relative price or costs, which is challengeable to generalize study results across countries.[25] Furthermore, in the present study the QALY gains were 0.47 versus 0.32 (base case) and cost savings were US $1,234 versus US $728 (base case) for the subgroup of NSAIDs naïve patients and all patients respectively. These results indicate that when *H. pylori* screening/eradication conducted among NSAIDs-naïve patients who required long-term NSAIDs treatment would effectively prevent PUD.[26-28]

H. pylori infection is known to be closely associated with a number of diverse gastrointestinal diseases such as gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancers,[29] and peptic ulcers.[30] In addition to *H. pylori*, the use of acetyl salicylic acid (i.e., aspirin) and NSAIDs, and smoking are also known to be risk factors for PUD. General population attributable risk for *H. pylori* was highest (48%) followed by the use of NSAIDs (24%) and smoking (23%).[31] The risk of peptic ulcer might be much higher for both *H. pylori* infection and NSAIDs administration in subjects with either *H. pylori* infection or NSAIDs-associated damage to the mucosa, because the mechanism of action is different. While NSAIDs induce prostanoid inhibition and nitric oxide mediated neutrophil recruitments into the microvasculature through topical and systemic

effects, *H. pylori* infection induces an inflammatory response in the mucosa.[32] Synergistic and additive effects of *H. pylori* infection and NSAIDs on the mucosa are possible. However, *H. pylori* screening/eradication in the chronic users of NSAIDs/aspirin are still optional instead of mandatory and are not covered by medical insurance provided by the South Korean government.[9] Thus, *H. pylori* screening/eradication is not routinely performed in clinical practice in South Korea. Furthermore, there are some drawbacks for that. Side-effects such as diarrhea, vomiting, nausea, abdominal pain, and abdominal bloating frequently develop during *H. pylori* eradication, resulting in poor patient compliance, eradication failure, and antimicrobial resistance.[33-35] However, the present study clearly demonstrated the cost saving associated with *H. pylori* screening/eradication, for the first time in a South Korean population.

This study had several limitations. First, we used meta-analysis results to determine the rates of ulcers and ulcer-related complications among NSAIDs or aspirin users depending on *H. pylori* eradication. We tried to find additional journals which deal with transition probability for PUD development under similar condition of our study design, but we could not find additional article after this meta-analysis result. Nonetheless, this meta-analysis included two China studies among five studies,[26,27] which are very higher *H. pylori* infection rate like our country. In addition, these reports included the case of endoscopic ulcer instead of clinical ulcers. Actually clinical ulcers are the ones that ultimately will likely transition to ulcer complications and the risks of bleeding and perforation. However, the differentiation of clinical ulcers from endoscopic ulcers looks like very difficult especially when transition probability for PUD development is under two conditions with or without long-term use of NSAIDs and/or aspirin. Second, the present study was based on the annual medical costs for ulcers and ulcer-related complications, around US $900 and US $2,400, respectively,[19] which is much lower than those in Western countries. The annual medical cost for treating PUD in the United States is US $24,000.[36] If the medical cost is very low to treat disease as like the situation of South Korea, universal prevention strategies may not be cost-effective from an economic perspective. However, our study clearly demonstrated the cost-effectiveness associated with *H. pylori* screening/eradication, for individuals taking NSAIDs or aspirin. Finally, we did not account for side effects of *H. pylori* eradication, such as gastrointestinal disorders, in the cost-effectiveness analysis. Since these symptoms are mild and can be reduced with supplementary probiotic therapies,[35] we assumed that they did not influence QALY.

In conclusion, the present study found that the *H. pylori* screening/eradication strategy was less expensive and more effective compared to the no-screening strategy. This was more apparent in younger individuals. Our results may help establish strategies for *H. pylori* screening in patients who required treatment with NSAIDs or aspirin in areas of endemic of *H. pylori* infection such as South Korea.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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