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ORIGINAL ARTICLE

Cost-effectiveness of alginic acid in combination with proton pump inhibitor for the treatment of gastroesophageal reflux disease in systemic sclerosis patients

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Abstract

Background: Systemic sclerosis (SSc) patients often become refractory to proton pump inhibitors (PPI)—a standard treatment for gastroesophageal reflux disease (GERD)—and intolerant to PPI in combination with domperidone. PPI with alginic acid is an alternative treatment option, but alginic acid is costly.

Objectives: We compared the costs and effectiveness of alginic acid plus PPI versus standard treatments (PPI with/without antacids as needed and lifestyle modifications) for GERD in SSc patients unsuitable for, or intolerant to, domperidone.

Methods: An economic evaluation using the Markov model was conducted among SSc patients aged between 40 and 65 years with GERD, having a partial or non-response to 4 weeks of standard-dose omeprazole (40 mg/day) and being unsuitable for or intolerant to domperidone. Using a societal perspective, we computed the incremental cost-effectiveness ratios (ICERs) in terms of Thai baht (THB) per quality-adjusted life-year (QALY) between a combination of alginic acid plus PPI and standard treatment for GERD. The lifetime time horizon was used.

Results: The ICER for alginic acid plus PPI versus standard treatments was 377 101 THB/QALY. According to the one-way sensitivity analysis, the cost of alginic acid was the most impactful parameter. If the market prices of alginic acid plus PPI were reduced by 61%, this treatment option would become cost-effective at the willingness-to-pay threshold of 160 000 THB/QALY (34.68 THB/USD data on 25 May 2023). Furthermore, if alginic acid were included in the public health insurance program, the national budget would be increased by 66 313 THB per patient, resulting in an overall budget increase of 5 106 101 to 8 885 942 THB compared with the standard treatment.

Conclusions: Alginic acid plus PPI does not represent good value for money compared with the standard treatment among such SSc patients in Thailand unless its price is reduced significantly.

KEYWORDS
alginic acid, cost-effectiveness, domperidone, economic, gastroesophageal reflux diseases, proton pump inhibitors, quality indicator and health care, quality of life, scleroderma and related disorders, systemic sclerosis

1 | INTRODUCTION

Systemic sclerosis (SSc) is a systemic connective tissue disease characterized by skin thickening and collagen deposition in internal organs. In addition, gastrointestinal tract involvement has been reported in SSc—with a prevalence between 54% and 90%: this involvement trends to high morbidity.[1,2] The most frequent complication of SSc involves the esophagus (range 30%–96% of cases).[2–6] One-third (34%) of patients have esophageal involvement at onset and 40% during follow up.[6] Gastroesophageal reflux disease (GERD) is the most common problem in SSc, with a prevalence of 60%–70%.[7–9] GERD can present in both the diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc) subsets.

Treatments for GERD among SSc patients are effectively no different from GERD treatments in non-SSc patients. Daily administration of a proton pump inhibitor (PPI) constitutes effective therapy;[10] but PPI (omeprazole) partial response GERD has been reported in around 54% of SSc patients.[10] The definition of PPI partially responsive GERD in the study was the severity of reflux symptoms and the frequency of symptom improvement under 50% after 4 weeks of omeprazole treatment compared with baseline data. The mean age of those with partially responsive GERD was 55.0 ± 9.8 years and dysphagia—esophageal dysmotility—was the only significant predictor of PPI partially responsive GERD.[10] The rate of complete response is increased by increasing the dosage of PPI,[11] or by adding prokinetics, alginic acid, or an anti-anxiety drug.[12–14]

Domperidone in combination with PPI for refractory GERD in SSc is a treatment option for those with partial response to PPI.[12] This regimen is common practice because of its low cost and is available under all public health insurances. However, patients who were intolerant to domperidone (i.e., with galactorrhea, cardiac arrhythmia) may not be suitable. Alternatively, Algycon—an alginic acid in chewing tablet form with viscous foam suspension of the antacid[15]—in combination with PPI can be a treatment choice for patients with partial response to PPI and in those who are unsuitable for domperidone; research suggests an equal clinical outcome to PPI plus domperidone.[12] However, alginic acid is comparatively expensive and currently unavailable for reimbursement under most public health insurance schemes in Thailand.

The current evidence indicates that alginic acid is an effective treatment for GERD in SSc. This study therefore aimed to complete a cost-effectiveness analysis of alginic acid plus PPI compared with standard treatment for GERD (i.e., PPI with/without antacids as needed plus lifestyle modifications) in SSc patients unsuitable for or intolerant to domperidone treatment. The study also sought to determine the budget impact of including alginic acid for treating GERD in SSc patients under the public health insurance schemes in Thailand.

2 | MATERIALS AND METHODS

2.1 | Research setting

A model-based economic evaluation was conducted using an SSc patient cohort who were between 40 and 65 years of age, with GERD, had partial or no response to 4 weeks of treatment of omeprazole standard dose, and were unsuitable for, or intolerant to, domperidone. The treatment combined alginic acid and standard-dose PPI (generic omeprazole), and the comparator was generic omeprazole alone. Lifestyle modifications and antacids were recommended as needed in both groups (PPI with/without antacids as needed plus lifestyle modifications).

2.2 | Model structure and parameters

The Markov state-transition model was applied to estimate all alternative policy choices, costs, and health outcomes (Figure 1). The time horizon was a lifetime for both sensitivity and base-case analyses. The cycle length of 12 weeks aligned with the follow-up period in real-world clinical practice. The costs and possible outcomes that could be achieved in the future were adjusted to the present value by using an annual discount rate of 3%.

The transition state included symptomatic GERD, GERD remission, and death. Transitional probability from the state of stability in symptomatic GERD and GERD remission to symptomatic GERD were drawn

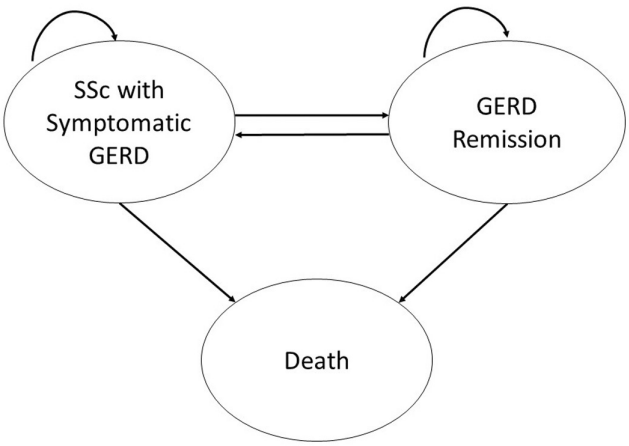

FIGURE 1 Markov model.

from literature reviews. At the same time, the state of symptomatic GERD to death and GERD remission to death were analyzed from a cohort of 502 SSc patients in Thailand. The cohort included in the analysis of transitional probability was conducted among SSc patients over 15 years of age, who attended and were followed up at Scleroderma Clinic, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand since 2013. All the patients in the cohort had a diagnosis of SSc based on the American College of Rheumatology (ACR) criteria and/or they fulfilled the classification criteria for SSc per the ACR/ European Alliance of Associations for Rheumatology (EULAR) 2013.[16] The probability of the transitional state of stability in symptomatic GERD was from the data of Foocharoen et al.,[10] who reported that around 54% of Thai SSc patients with GERD (131 from 243 cases) remained symptomatic for GERD without clinical improvement after treatment with omeprazole 20 mg twice daily for 4 weeks. However, no data on recurrent GERD after treatment were reported in the study. Hence, the transitional probability of GERD remission to symptomatic GERD was from the study by Lei et al.,[17] who conducted a prospective follow-up analysis of the predictors of recurrent GERD in non-SSc patients. The authors reported the recurrent rate of GERD at 30.4% (89 from 293 cases) during follow up. We therefore assumed that the probabilities of death among symptomatic GERD and GERD remission health states were equal because GERD did not directly affect mortality in SSc patients.

The cohort of SSc patients was obtained from Srinagarind Hospital, Khon Kaen University, between January 2013 and December 2020. All patients were diagnosed with SSc based on the ACR criteria[16] and/or the ACR/EULAR 2013 classification criteria of systemic sclerosis.[18] SSc is classified as the limited or diffuse subset per LeRoy et al.[19] The definition of GERD was fulfilled when the patient complained of heartburn and/or regurgitation.[9] Heartburn was defined by a burning sensation or discomfort behind the sternum extending to the neck (worse after meals or reclining) and improved by antacids.[20] Regurgitation was the perception of the flow of refluxed gastric contents into the mouth or hypopharynx.[20] GERD remission was defined when the patients reported no progression or exacerbation of GERD symptoms. We excluded patients receiving PPI other than generic omeprazole, diagnosed with GERD before the onset of SSc, and presenting overlap with other connective tissue diseases.

The cohort's start-date was the time of SSc onset. The end-date was the death date if the patient died; otherwise, it was the last meeting date of the patient in case the patient was lost to follow up or the patient was still alive at the end-date (31 December 2020). The survival time was measured according to the follow-up interval between the start- and end-dates. Time-to-event (death) was calculated by subtracting the end-date from the onset-date of SSc.

There is only one recent randomized controlled trial (RCT) of the efficacy of alginic acid for GERD treatment in SSc. The study compared the efficacy of alginic acid and domperidone add-on therapy for PPI partial response GERD in Thai patients with SSc.[12] However, there is currently no report of a head-to-head comparison of the efficacy between alginic acid plus PPI and standard therapy for GERD in SSc. In addition, there is only a prospective study of the efficacy of standard treatment for GERD with quality-of-life evaluation and adequate sample size in SSc by Foocharoen et al.[10] Therefore, the data on the efficacy of alginic acid plus PPI were extracted from the RCT study.[12] The efficacy of standard treatment for PPI partially responsive GERD was from a prospective study of the efficacy of standard treatment in 243 SSc patients by Foocharoen et al.[10]

The PPI partially responsive GERD was defined when the severity of reflux symptoms (assessed by visual analogue scale) and the frequency of GERD symptoms (evaluated using the Frequency Scale for the Symptoms of GERD) improved by less than 50% 4 weeks after treatment.[10] The efficacy was evaluated regarding symptom relief and quality of life determined by the EQ-5D score. The risk ratio of the patients persisting in a GERD state was 0.29, which was calculated from the proportion of the patients with non- or partial response to alginic acid plus PPI treatment and the proportion of the patients with non- or partial response to standard treatment.[10,12] The raw data of the EQ-5D score from both RCT and prospective studies were collected, and the utility score in each transition state and treatment was calculated using the EQ-5D, according to the data for estimating the EQ-5D Health States under population-based values in Thailand.[21] The utility scores of standard treatment and alginic acid treatment were comparable at baseline according to the baseline of the disease status of GERD with a utility score of 0.816.[10] The utility score after standard treatment was defined as those having a partial PPI GERD response before starting alginic acid treatment whereas the utility score after alginic acid treatment was the score after 4 weeks of combining PPI and alginic acid—based on data from an RCT comparing the effectiveness of PPI add-on therapy with domperidone and alginic acid.[12] The utility score of SSc with GERD—defined as a partial response or non-response to standard-dose PPI—was 0.804, and the utility score of GERD remission was 0.871.

The cost was calculated and evaluated based on a base case analysis. The direct medical cost, including the costs of alginic acid and standard treatment, were collected and extracted from the Cost Unit, University Hospital, Khon Kaen University. The indirect medical costs (transportation, food expenses, and productivity loss of the patients and their relatives) were collected through patient interviews, which were conducted for 63 patients between July 2021 and February 2022.

The parameters that were entered into the model are presented in Table 1. The distributions of parameters were (a) the parameter whose interval was between 0 and 1 (probability and utility) was in beta distribution; (b) the parameter whose interval was between 0 and positive infinity or skewed positively (cost data) was in gamma distribution; and (c) the parameter in a ratio (risk-ratio of the treatment response) was in log-normal distribution.

2.3 | Model simulation and sensitivity analysis

The budget impact analyses included societal variables, cost-effectiveness assessment, and healthcare payer's willingness to pay

TABLE 1 Parameters in the Markov model.

Variable	Distribution	Mean	95% CI	References and type of data
Transition probability at 3 months				
Stable on symptomatic GERD	Beta	0.539	0.474–0.603	Reference[10]
From symptomatic GERD to GERD remission	Beta	0.412		
From GERD remission to symptomatic GERD	Beta	0.087	0.073–0.101	Reference[17]
Stable on GERD remission	Beta	0.864		
From symptomatic GERD to death	Beta	0.049	0.040–0.058	502 SSc cohort data
From GERD remission to death	Beta	0.049	0.040–0.058	502 SSc cohort data
The risk-ratio of GERD event of alginic acid plus PPI compared to standard treatment	Log normal	0.29	0.13–0.59	Reference[10,12]
Cost[a] (THB/patient/3 months)				
1. Direct medical cost				
Cost of standard treatment				
Symptomatic GERD	Gamma	173.0	155.0–200.0	Hospital cost unit
GERD remission	Gamma	198.8	184.5–213.2	Hospital cost unit
Cost of alginic acid plus PPI treatment				
Symptomatic GERD	Gamma	6045.4	4233.9-7856.8	Hospital cost unit
GERD remission	Gamma	5553.3	3011.7-8095.0	Hospital cost unit
2. Indirect medical cost				
Transportation of patients and their relatives or caregivers	Gamma	960.3	891.7–1058.3	Patients interviewing
Food expense of patients and their relatives or caregivers	Gamma	403.3	301.9–468.4	Patients interviewing
Productivity loss of patients and their relatives or caregivers per day of a hospital visit	Gamma	396.5	370.5–422.6	Patients interviewing
Utility parameter				
Standard treatment				
Symptomatic GERD treatment	Beta	0.816	0.805–0.827	Reference[10]
GERD remission	Beta	0.804	0.787–0.821	Reference[12]
Alginic acid plus PPI				
Symptomatic GERD treatment	Beta	0.816	0.805–0.827	Reference[10]
GERD remission	Beta	0.871	0.850–0.892	Reference[12]

34.68 THB/USD data on 25 May 2023.

Abbreviations: 95% CI, 95% confidence interval; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; SSc, systemic sclerosis; THB, Thailand Baht.

(WTP), as recommended by the Thai Health Technology Assessment Guidelines.[22] The WTP threshold was set to 160 000 Thai baht (THB) (34.68 THB/USD data on 25 May 2023). A primary result was presented regarding the incremental cost-effectiveness ratio (ICER). The net monetary benefit was also calculated by converting health benefits (i.e., quality-adjusted life-years [QALYs]) into the standard metric of dollars using the country's WTP threshold. The cost associated with each treatment strategy was then subtracted, resulting in the net benefit of each strategy expressed in monetary units. The results and the Markov model were run and calculated using Microsoft Excel 2016.

A one-way sensitivity analysis was carried out by adjusting each base-case parameter to upper- and lower-bound values of its 95% confidence interval. The overall results were presented in a Tornado diagram. For a probabilistic sensitivity analysis, all parameters were randomly changed 1000 times using the Bayesian random technique to obtain 1000 replicated data sets. The results were presented as a cost-effectiveness plane and cost-effectiveness acceptability curves.

2.4 | Budget impact analysis

The budget impact analysis was calculated based on the step of a hierarchy approach (Figure 2). The step approach started with the total Thai population (age 40–65 years),[23] then the numbers of SSc patients in Thailand (https://ict.moph.go.th/th), the prevalence of GERD in SSc,[6–9] the prevalence of PPI partial responsive GERD,[10] the prevalence of domperidone side effects or non-responder,[12] and finally, a proportion of the population who are unable to be reimbursed from public health insurance schemes. The budget

impact analysis was considered for 5 years without discounting future costs.

3 | RESULTS

3.1 | Base case analysis

Alginic acid plus PPI offers more health benefits at a higher cost than the standard treatments at ICER of 377 101 THB/QALY (34.68 THB/USD data on 25 May 2023). The details of data from the base-case analysis are presented in Table 2.

3.2 | One-way sensitivity analysis

The cost of alginic acid plus PPI was the most impactful parameter in the one-way sensitivity analysis, followed by the utility vis-à-vis GERD remission after alginic acid plus PPI treatment and the utility of GERD remission after standard treatment. The ICER ranged from 214 822 THB/QALY to 539 379 THB/QALY according to varying the cost of alginic acid plus PPI and from 286 493 THB/QALY to 557 374 THB/QALY according to varying the utility of GERD remission of alginic acid plus PPI treatment. When the cost of alginic acid plus PPI was reduced by 61%, alginic acid plus PPI became cost-effective at the WTP threshold of 160 000 THB. The parameter with the least impact on ICER in the one-way sensitivity analysis was the direct medical cost of standard treatment, with the ICER ranging from 377 412 THB/QALY to 376 634 THB/QALY. The variation in the direct medical cost of standard treatment had relatively minimal influence on the ICER. The parameters affecting ICER are presented in descending order in Figure 3.

3.3 | Probabilistic sensitivity analysis

The incremental cost and effectiveness result from the 1000 simulations is presented as the Cost-effectiveness plane (Figure 4). The standard treatment was the reference treatment at a fixed point (0,0). Each point in the scatter plot represents one bootstrap simulation. After the 1000 simulation process of the incremental cost, the scatter plot and incremental QALY were greatest in the upper quadrants and comparable between the right and left upper quadrants. The findings indicate that treatment with alginic acid plus PPI was more expensive than the standard treatment but it is relatively as effective as standard treatment.

The cost-effectiveness acceptability curves from the probabilistic sensitivity analysis show the relationship of the probability of each treatment being cost-effective versus the ceiling threshold per one QALY gained. At the threshold of 160 000 THB/QALY, the probability of the treatment with alginic plus PPI being cost-effective was only 0.1 (or 10%). The results indicate that in only 10% of the simulations, the treatment with alginic acid plus PPI became cost-effective at this threshold. However, alginic plus PPI treatment showed a more favorable cost-effective when the ceiling threshold was set higher, at more than 360 000 THB/QALY. The cost-effectiveness curves from the probabilistic sensitivity analysis are presented in Figure 5.

3.4 | Budget impact analysis

The budget for 5 years of the treatment of alginic acid in combination with PPI was 92 120 THB per case and was 66 313 THB higher than the standard treatment. Based on the hierarchy approach of the budget impact analysis, a 5-year incremental budget

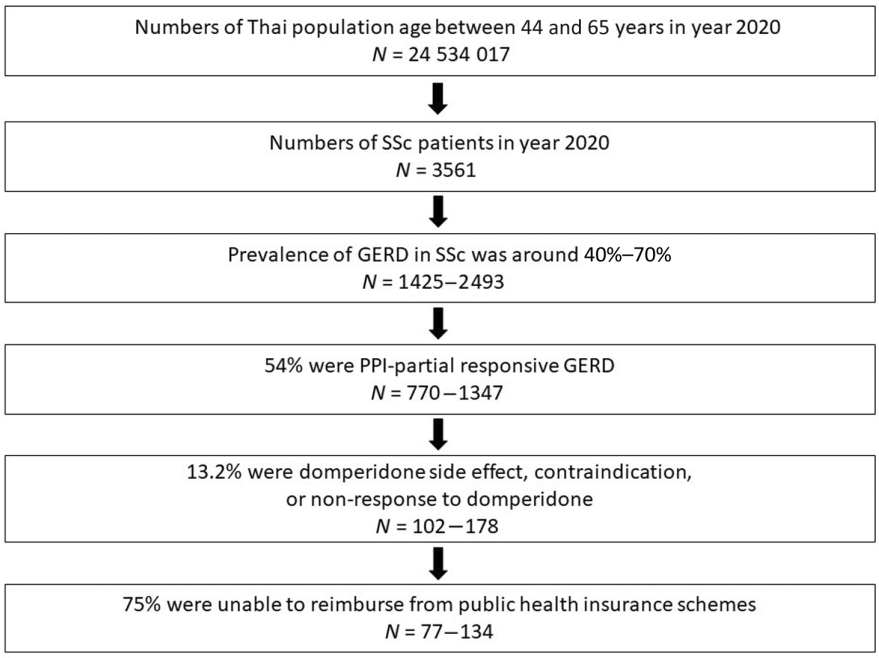

FIGURE 2 Hierarchy of step approach for budget impact analysis.

TABLE 2 The details of data from the base case analysis.

Item	With non-discount		With a 3% discount	
	Standard treatment	Alginic acid plus PPI	Standard treatment	Alginic acid plus PPI
Total cost	42783	153183	38106	136511
QALY	3.939	4.231	3.489	3.746
Cost difference	110400		98405	
QALY gain	0.293		0.257	
ICERs	377101		382186	

Abbreviations: ICERs, incremental cost-effectiveness ratios; PPI, proton pump inhibitor; QALY, quality-adjusted life-years.

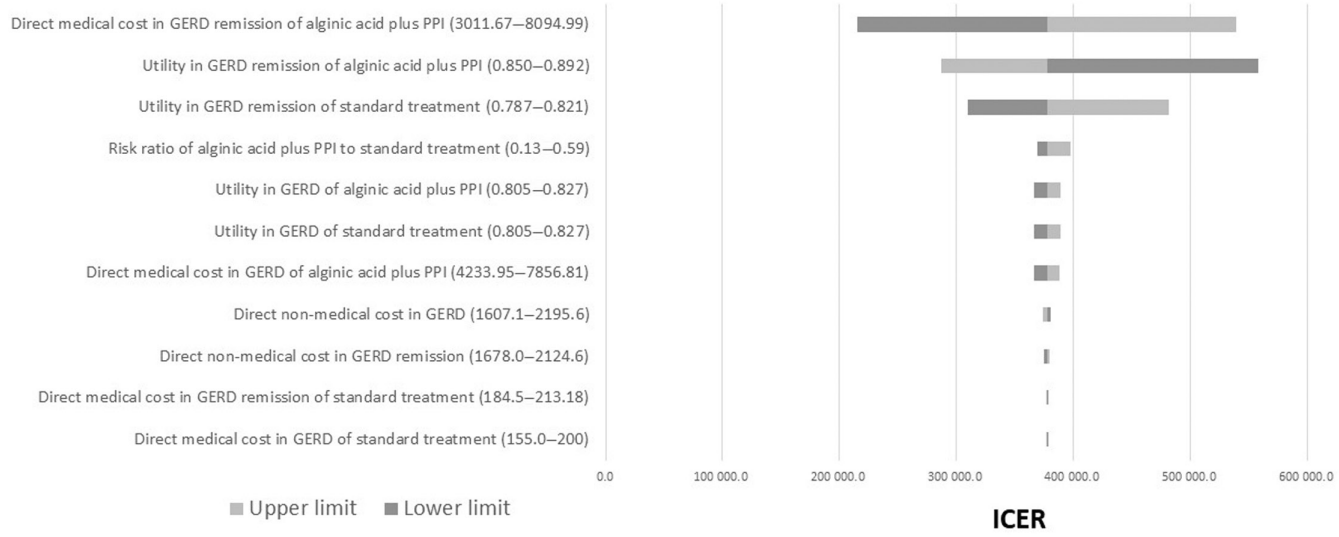

FIGURE 3 One-way sensitivity analysis.

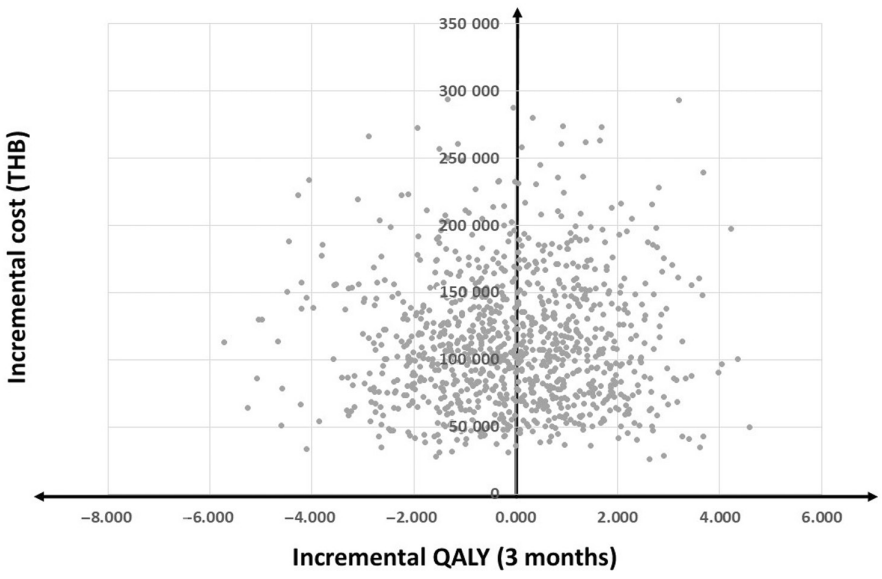

FIGURE 4 Cost-effectiveness plane.

of alginic acid in combination with PPI over the standard treatment was 5 106 101–8 885 942 THB. The budgets of alginic acid plus PPI and standard treatment from year 1 to year 5 are presented in Figure 6.

In a scenario with a 61% cost reduction of alginic acid in combination with PPI, the incremental budget over the standard treatment for the 5 years was reduced from 2 154 768 THB to 3749 856 THB.

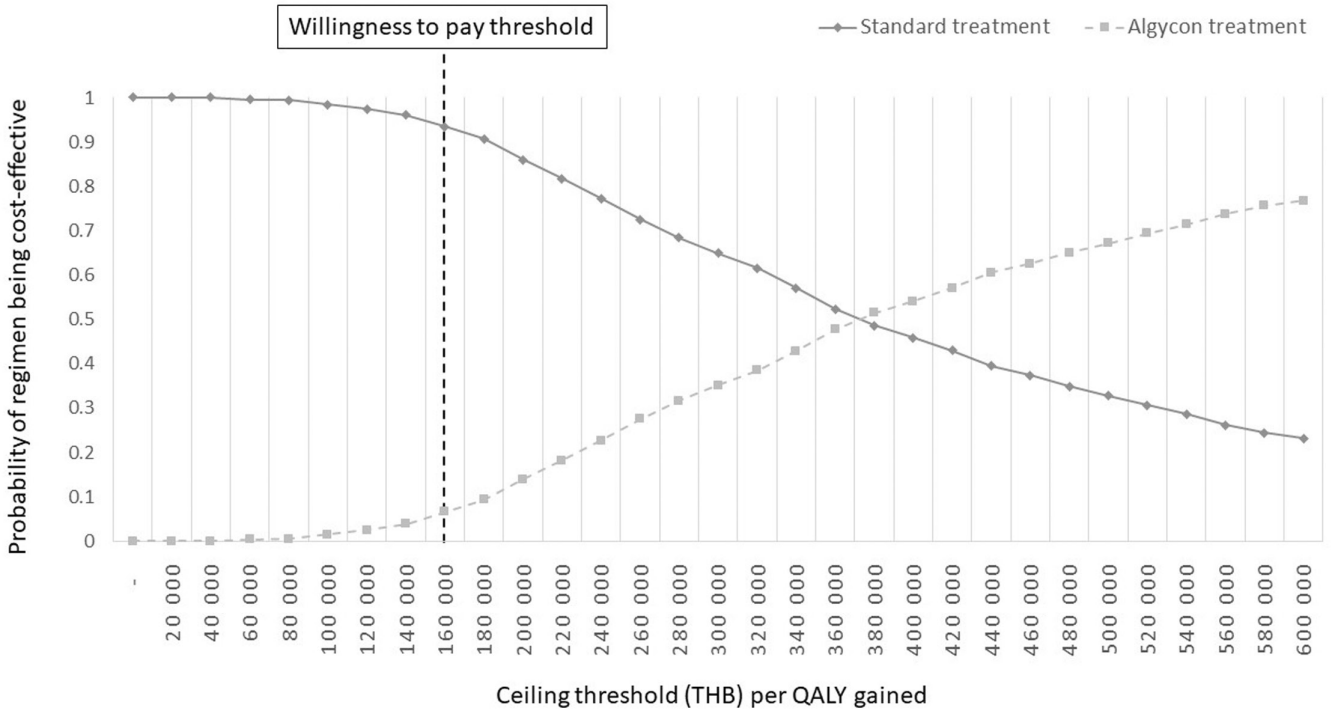

FIGURE 5 Cost-effectiveness acceptability curve.

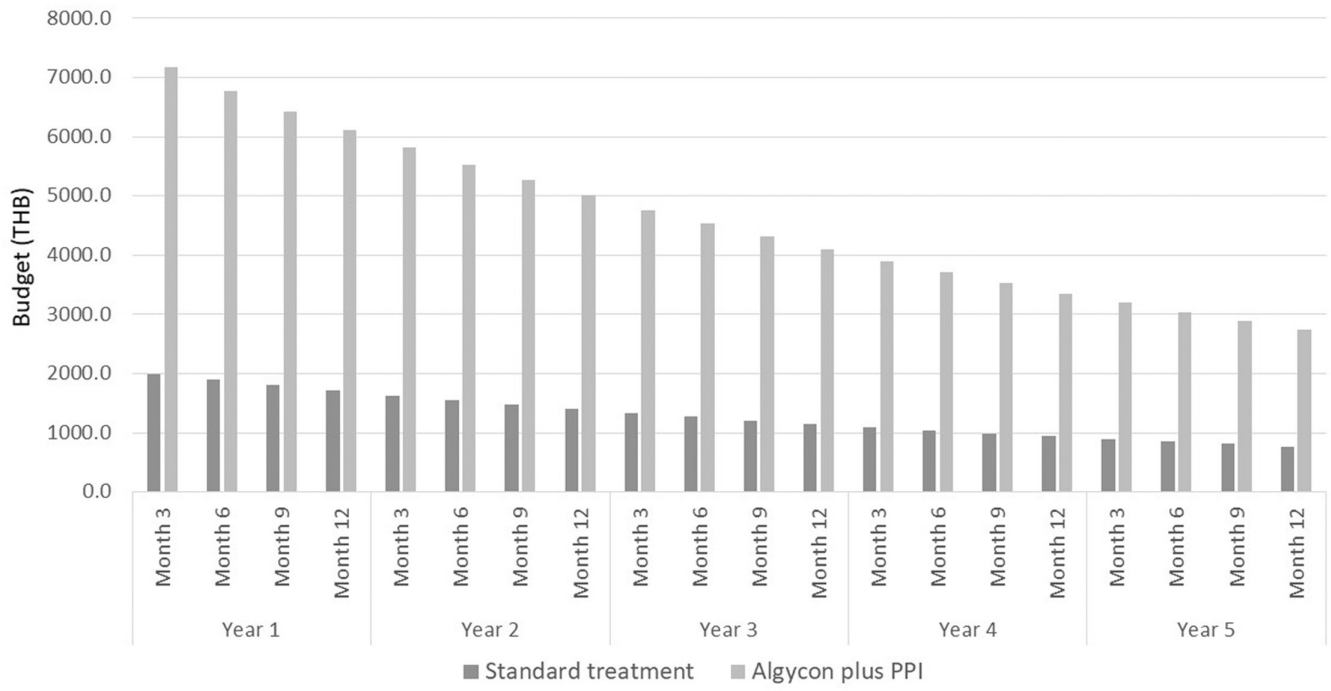

FIGURE 6 Budgets for 5 years of treatment of alginic acid in combination with protein pump inhibitors and standard treatment.

4 | DISCUSSION

To the best of our knowledge, this is the first cost-effectiveness study on GERD treatments in SSc patients, including alginic acid plus PPI. However, the cost of GERD treatment in the general population[24–27] and cost-effectiveness analysis of PPI and histamine 2 receptor antagonist were previously reported among Canadians with erosive esophagitis.[28] Our analysis indicates that alginic acid plus PPI was cost-ineffective compared with the standard therapy at the WTP threshold of 160 000 THB. Moreover, even if the WTP was set similar to the one applied in the study of Nimdet and Ngorsuraches[29] at 244 720 THB/QALY, alginic acid plus omeprazole

treatment remains cost-ineffective. However, alginic acid plus PPI can become cost-effective if alginic acid plus PPI costs are reduced by 61% of the current price in Thailand. This is in line with the sensitivity analysis, which indicates the cost of alginic acid plus PPI, utility in GERD remission of alginic acid plus PPI treatment, and utility of GERD remission of standard treatment are the most critical factors contributing to the value for money of the treatment. The findings were also in line with the study of Chen et al., who conducted a systematic review of the economic burden in SSc. The authors found that there was a cost variation among countries and the cost of medication had a large impact on the economic burden in most countries.[30]

Although alginic acid plus PPI does not represent value for money, SSc is a rare disease, and only 100–200 patients need the treatment. The 5-year budget required for the treatment is approximately 70000THB/case or 5–9 million THB overall. This financial requirement is minimal compared with the total health budget in Thailand, which is approximately 500000 million THB annually. We believe that if alginic acid plus PPI were included under the Thai public health insurance schemes, the regimen would offer clinical improvement of GERD in SSc patients who are in partial or non-response to omeprazole standard-dose but are unsuitable for or intolerant to domperidone. As such, we recommend that the Thai government negotiate drug prices with the company using the study results and consider including this treatment regimen in the public health insurance schemes.

The combination of PPI with either domperidone or algycon is effective for controlling GERD symptoms, but around 17% of the patients do not respond to the treatment according to the literature.[12] In cases that are refractory to all medical treatments for GERD, surgical treatments such as gastric fundoplication, ablative endoscopic techniques, transoral incisionless fundoplication, or magnetic sphincter augmentation might be required as an option of alternative treatment for GERD.[31] According to the high incidence of postoperative dysphagia and high recurrence rate after gastric fundoplication in SSc with GERD,[32,33] the surgical treatment, therefore, is not recommended or constitutes a relative contraindication in SSc patients. We, therefore, did not include the cost of surgical treatment in the analysis.

Endoscopy can help to confirm esophagitis-associated GERD when therapy fails,[34] and/or evaluate the complication of GERD such as esophageal stricture, Barrett's esophagus, and esophageal cancer.[32,35–37] However, endoscopy is an invasive procedure, and there were limitations to performing the procedure in SSc patients, particularly in the dcSSc subset with limited mouth opening ability or desaturation from interstitial lung fibrosis. Hence, endoscopy is not routinely performed in our SSc patients with GERD. We, therefore, did not evaluate the cost of endoscopy in the analysis.

Hospitalization cost was not included in the analysis because GERD does not commonly require hospitalization. On the other hand, interstitial lung disease (ILD)—a common indication of hospitalization and mortality risk—was associated with GERD in SSc. Therefore, it is uncertain whether ILD that can result in hospitalization is related to GERD or ILD could be a feature of lung involvement by SSc itself. We, therefore, did not include the hospitalization cost in the analysis.

Regarding on future research, we consider that RCT or pragmatic trials assessing the efficacy of alginic acid plus PPI versus PPI with and without antacids, and lifestyle modification are the most important studies to be conducted followed by a quality of life study of patients with active disease and patient response to treatment. Although, the direct medical cost in the intervention arm appears to be the most prominent variable in the univariate sensitivity analysis, these data can be easily obtained from the RCT or pragmatic trial, making it accessible for further analysis and decision-making.

There are some limitations to the current study. First, no high-potency PPI was analyzed as a comparator for evaluating cost-effectiveness for GERD in SSc because high-potency PPI is a high-cost medicine and not available for reimbursement under most health insurance schemes in Thailand. In addition, we believed that adding a medication having other mechanisms of action, such as prokinetics or alginic acid, might alleviate GERD symptoms more than switching to a medicine with high-potency but having the same mechanism of action. Second, the standard treatment costs in GERD remission might not be valid. The cost was calculated according to the PPI plus aluminum hydroxide on demand, so the cost in each visit varied by the prescription of aluminum hydroxide, which might explain why the cost of standard treatment in GERD remission was greater than for symptomatic GERD. Third, the risk ratio of a GERD event of alginic acid plus PPI compared with standard treatment was applied by using the proportion of treatment response of alginic acid plus PPI and treatment response of standard treatment. This is because no study to date has included a head-to-head comparison between the efficacy of standard treatment and the efficacy of alginic acid plus PPI treatment for GERD in SSc. Consequently, the risk ratio might not represent the exact efficacy of those treatments.

AUTHOR CONTRIBUTIONS

CF designed the study, conducted data collection and analysis, and drafted the manuscript. PK and YT designed the study, performed data analysis, and edited and proofread the manuscript. AM and SS collected data, participated in the study, and proofread the manuscript. WM and JC participated in the study and proofread the manuscript. AS designed the study, performed data analysis, and edited, proofread, and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The Human Research Ethics Committee of Khon Kaen University reviewed and approved the study per the Helsinki Declaration and the Good Clinical Practice Guidelines (HE641365). In addition, all eligible patients signed informed consent before entry into the study.

CONSENT FOR PUBLICATION

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