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# Health Economics Evaluation of Diagnostic Strategies for Gastroesophageal Reflux Disease with Reflux Symptoms in China

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# Health Economics Evaluation of Diagnostic Strategies for Gastroesophageal Reflux Disease with Reflux Symptoms in China

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## Abstract

**Objectives:** The gold standard and algorithmic approach for the diagnosis of gastroesophageal reflux disease (GERD) are not yet defined. We compared the two recommended diagnostic processes using a Chinese population-based health economics analysis.

**Methods:** Our analysis considered a hypothetical cohort of patients with typical reflux symptoms. We constructed a decision tree model to compare the two recommended diagnostic processes described in American College of Gastroenterology (ACG) clinical guidelines (stratified endoscopy strategy) and Chinese expert consensus (endoscopy-first strategy). The first strategy begins with hazard stratification based on alarm symptoms. Patients with alarm symptoms directly undergo endoscopic examination, while patients without alarm symptoms receive proton pump inhibitor as diagnostic treatment. In the second strategy, all patients with reflux symptoms complete an endoscopic examination. Sensitivity analysis was performed to evaluate a range of cost and probability estimates on costs and health outcomes over a one-year time horizon from the health care system perspective.

**Results:** The total expected costs were $122.51 for the stratified endoscopy strategy and $150.12 for the endoscopy-first strategy. The ICER comparing the endoscopy-first strategy with the stratified endoscopy strategy was $440.39 per additional correct case of GERD. The rates of detecting upper gastrointestinal CA of the two strategies were 0.0088 and 0.0120, and the ICER was $8561.34.

**Conclusions:** The use of endoscopy for all patients with reflux symptoms was more effective but with an increased cost compared with the strategy recommended in international guidelines.


Key Words: Gastroesophageal reflux disease; Endoscopy; Reflux symptom; Cost-effectiveness analysis; Decision tree model

### Key questions

What is already known?

- In mainland China, the overall pooled prevalence of GERD showed an increasing trend.
- The Chinese expert consensus recommends endoscopy for all patients with reflux symptoms at the initial diagnosis because of the high incidence of upper gastrointestinal tumors and readily available gastroscopy at a low cost.

What are new findings?

- This study complemented gaps in health economics evidence for the expert consensus of GERD diagnosis in China.
- The use of endoscopy for all patients with reflux symptoms was more effective but with an increased cost.

What do the new findings imply?

- There still requires more targeted, higher-quality endoscopy strategies depending on the regional spectrum of diseases and accessibility of medical resources.

## INTRODUCTION

Gastroesophageal reflux disease (GERD) is a condition in which reflux of gastric contents causes troublesome symptoms and complications. Although heartburn and regurgitation are considered typical symptoms associated with GERD, a broad spectrum of other symptoms include dysphagia, chest pain, painful swallowing, and extraesophageal symptoms (e.g., chronic cough, hoarseness, laryngitis, pharyngitis, and pulmonary fibrosis).[1] The estimated global prevalence of GERD is 13% and varies considerably by region and population. In mainland China, the overall pooled prevalence of GERD was 8.7% and showed an increasing trend.[2,3] Considering the large population size of China, effective screening and management strategies for GERD are needed.

The diagnosis of GERD is commonly based on the combination of symptoms, endoscopic findings, reflux monitoring, and therapeutic response.[1] The gold standard and algorithmic approach for diagnosis are not yet defined. American College of Gastroenterology (ACG) clinical guidelines recommend starting with a proton pump inhibitor (PPI) among patients with typical symptoms.[4] For patients with alarm symptoms (such as dysphagia, weight loss, bleeding, vomiting, and/or anemia) or risk factors for Barrett's esophagus, endoscopy is strongly recommended as the first step for evaluating esophageal mucosa. In contrast, the Chinese expert consensus recommends endoscopy for all patients with reflux symptoms at the initial diagnosis.[5] The rationale is based on the fact that China is a country with a high incidence of upper gastrointestinal tumors and readily available gastroscopy at a low cost.[6-8] Early endoscopic examination is beneficial for tumor screening and assessment of disease status. A meta-analysis found that the tumor detection rate of endoscopy in patients with upper gastrointestinal symptoms at the initial consultation in Asia was 1.3%.[6] A study in Guangzhou reported a detection rate of 0.8% for esophageal and gastric cancers in patients with initial heartburn without alarm symptoms.[7] However, no study provides economic evidence for this strategy in China. Therefore, we compared the two recommended diagnostic processes described above using a Chinese population-based health economics analysis.

## METHODS

Our analysis considered a hypothetical cohort of patients with typical reflux symptoms (heartburn and regurgitation) in China. Our decision tree model incorporated base-case estimates of most likely clinical scenarios and then used sensitivity analysis to evaluate a range of cost and probability estimates on costs and health outcomes over a one-year time horizon from the health care system perspective. All analyses were performed using TreeAge Pro 2022 software.

### Decision Model

The decision model considered two strategies representing different diagnostic processes in international or Chinese guideline recommendations (Figure 1).

As recommended in international guidelines, the first strategy begins with hazard stratification based on alarm symptoms, including dysphagia, weight loss, gastrointestinal bleeding, and persistent vomiting (stratified endoscopy strategy). Patients without alarm symptoms are considered at low risk of malignancy and receive PPI as diagnostic treatment. Ineffective PPI therapy is indicative of sequential invasive testing utilizing endoscopy and esophageal reflux monitoring. Patients with alarm symptoms directly undergo endoscopic examination, followed by a biopsy for suspected lesions. If no positive endoscopic results are found, a PPI test and esophageal reflux monitoring will be performed for next-step testing. Patients with reflux esophagitis (RE) or Barrett's esophagus (BE) confirmed by endoscopic

biopsy, positive PPI response, or reflux evidence from esophageal monitoring are diagnosed as GERD in this strategy. Peptic ulcer disease (PUD) and upper gastrointestinal carcinoma (CA) can also be detected during endoscopy examination. If endoscopy, PPI test, and reflux monitoring are negative, GERD is excluded.

The second strategy is based on an expert consensus in China, the endoscopy-first strategy. All patients first complete an endoscopic examination. The subsequent assessment algorithm is the same as that in the first strategy.

The biopsy is considered the gold standard for differentiating upper gastrointestinal lesions under endoscopy and esophageal monitoring for pathological reflux. We did not consider the potential side effects of PPI, complications of diagnostic procedures, or the impact of the diagnosis on quality of life or the subsequent utilization of healthcare resources.

**Clinical Inputs and transition probabilities**

Preference was given to the most recent studies based on the Chinese population. When more than one value of the same parameters was reported in multiple studies, the maximum and minimum values, or baseline±20% if insufficient parameters, were included as the value range. For unavailable parameters, data were obtained through expert consultation or referred to relevant studies from other countries. All input parameters are listed in Table 1.

**Disease prevalence.** Bai et al. conducted a large-scale retrospective analysis in a single tertiary medical center and demonstrated the symptomatic profile of patients undergoing upper endoscopy.[9] A total of 15,431 patients had regurgitation or heartburn, and 1,204 had alarm symptoms (7.8%). Common endoscopic lesions included RE, PUD, and BE, while CA was rarely detected. In patients with reflux symptoms but no alarm symptoms, the proportions of RE, PUD, and CA were 25.8%, 12.7%, and 0.7%, respectively.[10] However, no study has separately characterized endoscopic performance in patients with reflux and alarm symptoms. The results from all alarm symptom populations (12.5% RE, 17.9% PUD, and 7.7% CA under endoscopy) were used to estimate these parameters in our model.[10] For all patients with reflux symptoms, the proportions were calculated using the following formula:

*Probability of certain lesion in all patients = Probability of certain lesion in patients with alarm symptoms × Probability of alarm symptoms + Probability of certain lesion in patients without alarm symptoms × (1 - Probability of alarm symptoms)*

The detected rate of BE has been rarely investigated, and the approximate estimation of baseline values was obtained through a meta-analysis (total endoscopic detection rate 1.0%, 95% CI 0.1%-1.8%).[11] The proportion of patients without clinically significant endoscopic findings in this model was calculated from 1 minus the sum of other lesions.

**Diagnostic test characteristics.** The response rate of PPI over 2-8 weeks in patients with reflux symptoms ranged from 54.1% to 63.9%.[12-16] We chose the result of an RCT evaluating esomeprazole as the baseline.[14] The PPI test's pooled sensitivity, specificity, and positive predictive value from a previous meta-analysis were 0.52, 0.32, and 0.38, respectively.[17] Esophageal reflux monitoring was once considered the “gold standard” in many DTAs and guidelines. However, the diagnostic performance in Chinese patients was limited, and results varied widely.[18-21] Wang et al. retrospectively investigated 177 patients with typical reflux symptoms who received esophageal function tests, and 122 of them had AET>4%. In patients who did not respond to PPI, 50.0% had AET>4%. In patients without positive endoscopic findings, 65.9% had AET>4%.[18]

**Cost.** All costs were converted to US dollars using published exchange rates. Only direct healthcare

costs were considered. Costs for drugs and endoscopic and diagnostic procedures were referenced in terms of drug and medical service pricing in Peking Union Medical College Hospital. There was no time discounting of future costs and health outcomes as the period of the model was less than one year.

### Base-case analysis

The base-case analysis estimated the incremental cost-effectiveness ratio (ICER) between the stratified endoscopy strategy and the endoscopy-first strategy. We used the incremental cost per additional correct diagnosis of GERD. As a primary outcome measure for effectiveness, the correct diagnosis of GERD (including biopsy-confirmed RE and BE, NERD confirmed by reflux monitoring, and true positive results in the PPI test) was assigned a value of 1. When the final diagnosis was incorrect (false positive) or was determined as PUD, CA or other disorders, we assigned a value of 0. We also evaluated the incremental cost per additional detection of upper gastrointestinal CA (biopsy-confirmed CA was assigned a value of 1, while other results were 0). The result of cost-effectiveness analysis was only described in this study since there is no accepted willing-to-pay (WTP) threshold for ICER.

### Sensitivity Analysis

To evaluate the robustness of the results of the decision tree analyses, we explored broad distributions around uncertain parameters using one-way sensitivity analysis. Each parameter varied within the value range to explore the potential factors affecting the optimal strategy, and the results were shown in the tornado diagrams.

### Patient and Public Involvement

No patients were involved in the development of the research question or its outcome measures, the conduct of the research, or the preparation of the manuscript.

## RESULTS

### Base case analysis

The results of our base case analysis are presented in Table 2. The total expected costs were $122.51 for the stratified endoscopy strategy and $150.12 for the endoscopy-first strategy. The rate of correct diagnosis of GERD was 0.45 and 0.52 for the stratified strategy and the endoscopy-first strategy, respectively. The ICER comparing the endoscopy-first strategy with the stratified endoscopy strategy was $440.39 per additional correct case of GERD. The rates of detecting upper gastrointestinal CA of the two strategies were 0.0088 and 0.0120. The ICER was $8561.34. A total of 47.4% of patients underwent endoscopy, and 25.8% finished reflux monitoring in the stratified endoscopy strategy. In the other strategy, where all patients underwent endoscopy, 25.7% needed reflux monitoring.

### One-way sensitivity analyses

The one-way sensitivity analysis is shown in Figure 2. The most sensitive parameters were the probability of RE in patients without alarm symptoms, the probability of true positives in the PPI test, and the cost of endoscopy.

## DISCUSSION

There is an increasing trend of GERD globally, as well as in the Chinese population. However, the diagnostic processes still vary in different regions of the world.[2,4,5] The endoscopy-first strategy used in

China was more effective but also more expensive than the stratified endoscopy strategy recommended by international guidelines.

The Chinese expert consensus that prioritizes the recommendation of endoscopy is based on two main facts, the first of which is the risk of malignant lesions.[5] Upper gastrointestinal tract cancer (UGIC), including esophageal cancer (EC) and gastric cancer (GC), is prevalent in China.[29] In 2020, UGIC accounted for 11.38% and 15.97% of all new incidence cases and deaths from malignant tumors in China.[29] Endoscopic screening can reduce the incidence and mortality associated with UGIC.[30-33] Multiple economic evaluation studies from different countries indicated that endoscopic screening was cost-effective compared with no screening.[34-39] Xia et al. constructed a Markov model to evaluate the cost-effectiveness of endoscopic screening strategies for UGIC among people aged 40 to 69 years in areas of China where the risk of these cancers is high.[40] Combined endoscopic screening for EC and GC may be cost-effective, and screening every two years would be optimal. The use of endoscopy is common in China. According to the national gastrointestinal endoscopy census in 2020, from 2012 to 2019, the number of medical institutions conducting gastrointestinal endoscopies increased from 6,128 to 7,470; the number of practitioners had a growth rate of 51.27%, and a total of 38,730,000 cases of gastrointestinal endoscopy were carried out nationwide in 2019, representing an increase of 34.62% from 2012.

When we focused on diagnosing GERD or CA in this model, the endoscopy-first strategy showed increased effectiveness and more costs. The use of alarm symptom stratification avoided endoscopy in more than half of all patients, while the need for expensive reflux monitoring was comparable between the two strategies. Moreover, we noted that the proportion of CA in the reflux symptomatic population does not correlate with the traditionally high prevalence of upper gastrointestinal CA in China. In addition, chronic inflammation caused by GERD is one of the most critical risk factors for esophageal adenocarcinoma, while squamous carcinoma accounts for more than 80% of cases in China.[41] Therefore, the significance of reflux symptoms alone in suggesting upper gastrointestinal malignancies in the Chinese population still needs to be supported by large-scale studies.

According to the one-way sensitivity analysis, the first three factors affecting the baseline results of ICER were the probability of RE in patients without alarm symptoms, the probability of true positives in the PPI test, and the cost of endoscopy. Based on the literature search results, alarm symptoms are commonly used exclusion criteria when investigating endoscopic manifestations. RE is the most common lesion observed under endoscopy in patients with reflux symptoms, and the range of its probability was obtained from different single-centered research data covering the provinces of Guangdong, Shanghai, Beijing, and Xinjiang.[7,10,19,24,25] The lower limit of the range is further lowered using 80% of the baseline. For the diagnostic accuracy of the PPI test, pooled results and its 95% confidence interval from a meta-analysis were used as baseline and range.[17] However, these results are not specific to the Chinese population alone. These two parameters had wide enough ranges for sensitivity analysis, and none reversed the base-case result. But obviously, there is an eager need for large-scale nationwide epidemiological surveys. The price of endoscopes is another critical point to focus on. We used the pricing of endoscopes in Beijing hospitals as the basis, with a 20% upward and downward fluctuation as the range according to expert consultation. The real world is bound to be more complex, influenced by different regions, hospital grades, and health insurance policies.

In 1999, Ofman et al. compared the clinical and economic outcomes of the empiric trial of omeprazole and the traditional invasive strategy for diagnosing GERD as the cause of non-cardiac chest pain.[42] Results showed that the omeprazole test was related to reduced costs and improved diagnostic

certainty, providing a simple, cost-effective choice for common disorders in primary care settings. However, no cost-effectiveness studies compared different diagnosis strategies in patients with typical reflux. Compared to non-cardiac chest pain, reflux symptoms suggest different differential diagnoses and different significance in predicting malignancy, thus affecting patient treatment choices and outcomes. The stratified endoscopy strategy in this model used alarm symptoms as the rationale for hazard stratification. Additional factors are considered to identify high risk for malignant lesions, including region, family history, dietary habits, H. pylori infection, etc, which are potential to be included in further hazard stratification. Accurate risk stratification helps to highlight the value of endoscopy for precise screening and definite diagnosis rather than crude primary screening.

This study had some limitations. One of the significant limitations is the one-year time horizon. The study did not measure the costs and outcomes related to treatment, survival, and disability. Cost-effectiveness was not measured in terms of cost per disability-adjusted life year averted, which is a more robust measure of cost-effectiveness. Moreover, our model is structured based on several assumptions and parameter estimates. Parameter estimates were extracted from multiple sources with different evidence quality. Considering that the prevalence also varies considerably in various regions of China, these results are bound to change with changes in prevalence rates from other populations.

## CONCLUSION

This study provides economic evidence for the expert consensus of GERD in China. The use of endoscopy for all patients with reflux symptoms was more effective but with an increased cost compared with the strategy recommended in international guidelines. Diagnosing GERD while ruling out malignant lesions in the vastly outnumbered reflux population in China still requires more targeted, higher-quality endoscopy strategies depending on the regional spectrum of diseases and accessibility of medical resources.

**Figure legends:**

**Figure 1. Decision tree model.** RE, reflux esophagitis; PUD, peptic ulcer disease; BE, Barrett's esophagus; CA, carcinoma; PPI, proton pump inhibitors; NERD, non-erosive reflux disease; GERD, gastroesophageal reflux disease.

**Figure 2. Tornado diagram of ICER.** RE, reflux esophagitis; PUD, peptic ulcer disease; BE, Barrett's esophagus; CA, carcinoma; PPI, proton pump inhibitors.

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**Contributors:** XY and DW designed the study. XY, XL, YC, MO, ZG, CL, DY contributed to the conduction of the study. XY and XL collected the data. XY and XL performed statistical analysis and wrote the draft of the manuscript. HC and FX provided advices for the research protocol, statistical analysis plan and data analyses. HC, FX and DW reviewed and edited the manuscript. All authors read and approved the final manuscript.

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**Data sharing statement:** This study was based on published data. The data used for analyses are available and shown in table.

**Ethics approval:** This study used a decision tree model based on published data, and no ethics approval and informed consent were requested.

**Competing interests:** All the authors have no conflict of interest to declare.

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**Table 1. Model parameters**

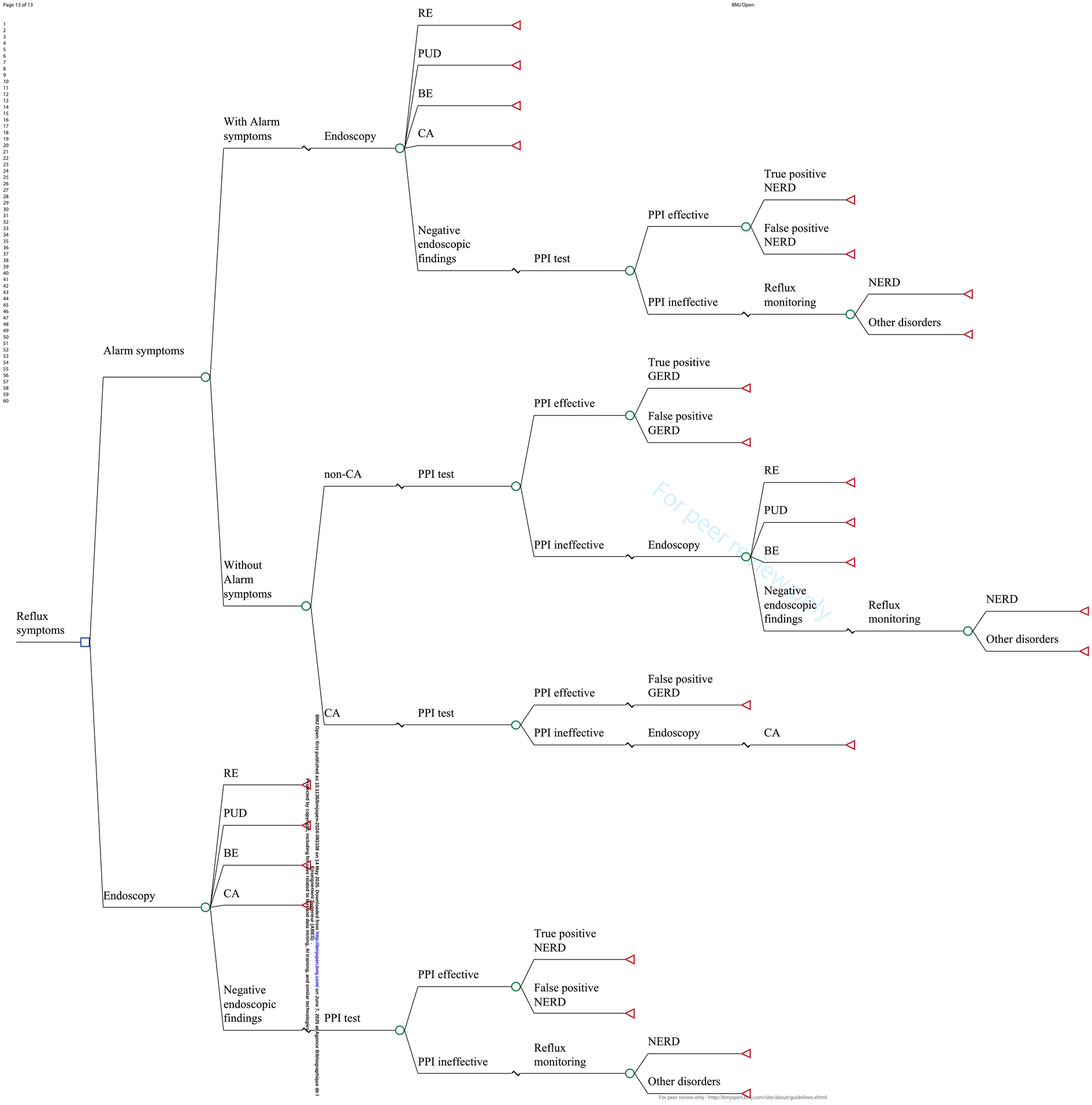
| Parameters | Baseline | Range | Reference |
|---|---|---|---|
| **Clinical probability** | | | |
| Proportion of patients with alarm symptoms | 0.078 | 0.062-0.270 | 9,10,22,23 |
| Response rate to PPI treatment | 0.571 | 0.457-0.685 | 12-16 |
| Probability of true positive in PPI test | 0.380 | 0.300-0.490 | 17 |
| Probability of positive reflux monitoring | 0.500 | 0.400-0.689 | 18,20 |
| **In patients with alarm symptoms** | | | |
| Probability of RE under endoscopy | 0.125 | 0.100-0.359 | 10.23 |
| Probability of PUD under endoscopy | 0.179 | 0.143-0.476 | 10,22,23 |
| Probability of BE under endoscopy | 0.010 | 0.001-0.018 | 11 |
| Probability of CA under endoscopy | 0.077 | 0.023-0.172 | 10,23 |
| **In patients without alarm symptoms** | | | |
| Probability of RE under endoscopy | 0.258 | 0.206-0.410 | 7,10,19,24,25 |
| Probability of PUD under endoscopy | 0.127 | 0.027-0.152 | 7,10,19,24 |
| Probability of BE under endoscopy | 0.010 | 0.001-0.018 | 11 |
| Probability of CA under endoscopy | 0.007 | 0.004-0.009 | 7,10,19,26 |
| **In all patients with reflux symptoms** | | | |
| Probability of RE under endoscopy | 0.248 | 0.102-0.298 | 10,27,28 |
| Probability of PUD under endoscopy | 0.131 | 0.068-0.157 | 10,27 |
| Probability of BE under endoscopy | 0.010 | 0.001-0.018 | 11 |
| Probability of CA under endoscopy | 0.012 | 0.010-0.017 | 10,27 |
| **Cost ($)** | | | |
| Cost of PPI[a] | 28.602 | 22.826-34.377 | |
| Cost of upper endoscopy | 56.378 | 45.103-67.654 | |
| Cost of endoscopic biopsy | 41.253 | 33.002-49.503 | |
| Cost of esophageal reflux monitoring | 233.760 | 187.010-280.520 | |

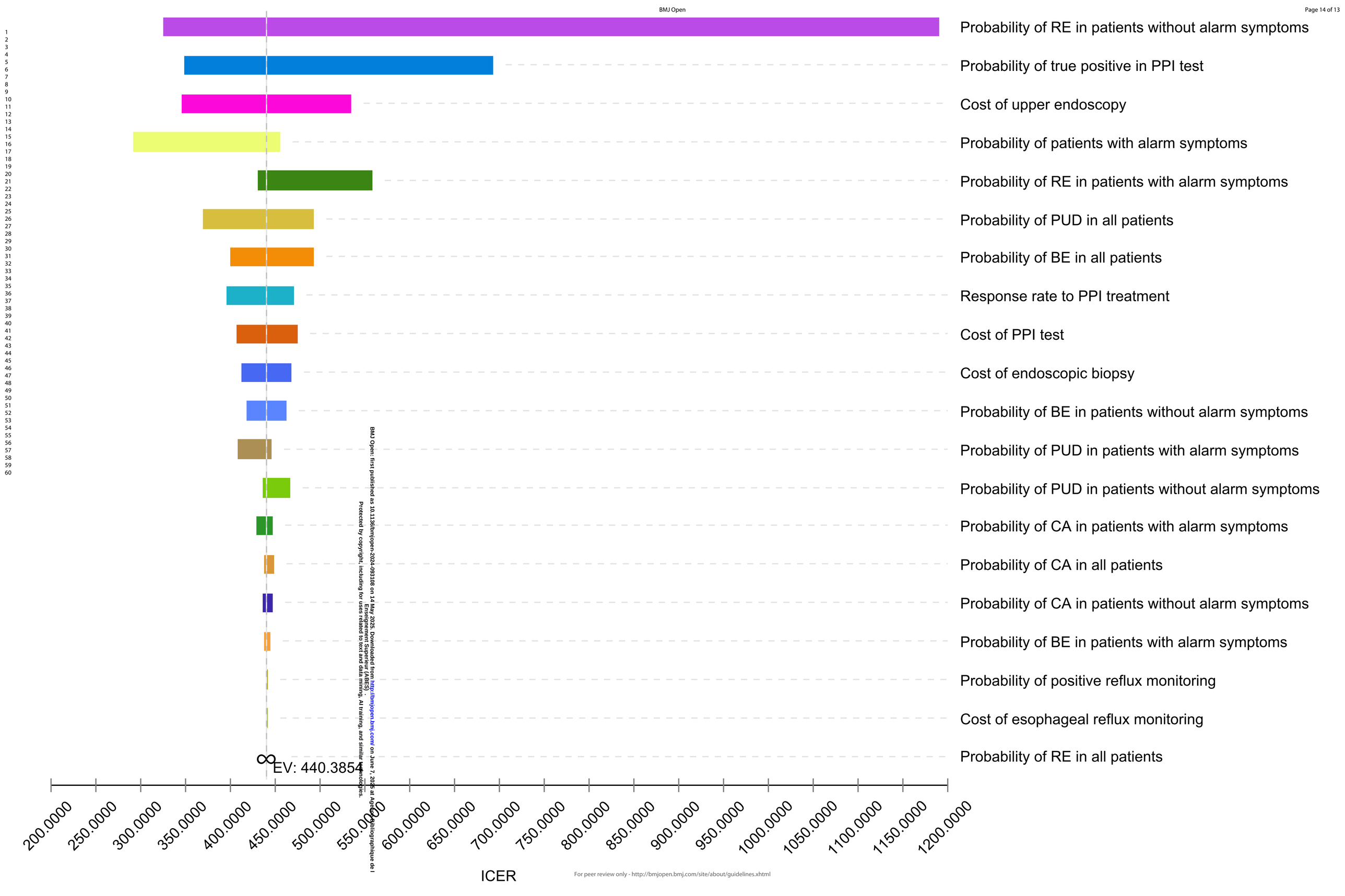
a. Omeprazole 20mg bid for two weeks. RE, reflux esophagitis; PUD, peptic ulcer disease; BE, Barrett's esophagus; CA, carcinoma; PPI, proton pump inhibitors.

**Table 2. Base-case analysis**

| Strategy | Cost ($) | Diagnosis of GERD | | Detection of CA | |
|---|---|---|---|---|---|
| | | Effectiveness | ICER | Effectiveness | ICER |
| Stratified endoscopy strategy | 122.5103 | 0.4538 | | 0.0088 | |
| Endoscopy-first strategy | 150.1226 | 0.5165 | 440.3854 | 0.0120 | 8561.3360 |

GERD, gastroesophageal reflux disease; CA, carcinoma; ICER, incremental cost-effectiveness ratio.





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# Health Economics Evaluation of Diagnostic Strategies for Gastroesophageal Reflux Disease with Reflux Symptoms in China: a Decision Tree Analysis

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# Health Economics Evaluation of Diagnostic Strategies for Gastroesophageal Reflux Disease with Reflux Symptoms in China: a Decision Tree Analysis

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## Abstract

**Objectives:** American College of Gastroenterology (ACG) and Chinese expert consensus recommended different algorithmic approaches for the diagnosis of gastroesophageal reflux disease (GERD) are not yet defined. We compared the two recommended diagnostic processes using a Chinese population-based health economics analysis.

**Methods:** Our analysis considered a hypothetical cohort of patients with typical reflux symptoms. We constructed a decision tree model to compare the two recommended diagnostic processes described in ACG clinical guidelines (stratified endoscopy strategy) and Chinese expert consensus (endoscopy-first strategy). The first strategy begins with hazard stratification based on alarm symptoms. Patients with alarm symptoms directly undergo endoscopic examination, while patients without alarm symptoms receive proton pump inhibitor as diagnostic treatment. In the second strategy, all patients with reflux symptoms complete an endoscopic examination. Sensitivity analysis was performed to evaluate a range of cost and probability estimates on costs and health outcomes over a one-year time horizon from the health care system perspective.

**Results:** The total expected costs were $122.51 for the stratified endoscopy strategy and $150.12 for the endoscopy-first strategy. The ICER comparing the endoscopy-first strategy with the stratified endoscopy strategy was $440.39 per additional correct case of GERD. The rates of detecting upper gastrointestinal CA of the two strategies were 0.0088 and 0.0120, and the ICER was $8561.34.

**Conclusions:** The use of endoscopy for all patients with reflux symptoms was more effective but with an increased cost compared with the strategy recommended in international guidelines.


Key Words: Gastroesophageal reflux disease; Endoscopy; Reflux symptom; Cost-effectiveness analysis; Decision tree model

### Strengths and limitations of this study

- ✓ Nationally representative data sources based on a particular population were used.
- ✓ Sensitivity analysis was done to determine the uncertainty in the estimates.
- ✓ Costs and outcomes related to treatment, survival, and disability were not measured.
- ✓ Regional differences among the Chinese population were not considered.

## INTRODUCTION

Gastroesophageal reflux disease (GERD) is a condition in which reflux of gastric contents causes troublesome symptoms and complications. Although heartburn and regurgitation are considered typical symptoms associated with GERD, a broad spectrum of other symptoms include dysphagia, chest pain, painful swallowing, and extraesophageal symptoms (e.g., chronic cough, hoarseness, laryngitis, pharyngitis, and pulmonary fibrosis).[1] The estimated global prevalence of GERD is 13% and varies considerably by region and population. In mainland China, the overall pooled prevalence of GERD was 8.7% and showed an increasing trend.[2,3] Considering the large population size of China, effective screening and management strategies for GERD are needed.

The diagnosis of GERD is commonly based on the combination of symptoms, endoscopic findings, reflux monitoring, and therapeutic response.[1] American College of Gastroenterology (ACG) clinical guidelines recommend starting with a proton pump inhibitor (PPI) among patients with typical symptoms.[4] For patients with alarm symptoms (such as dysphagia, weight loss, bleeding, vomiting, and/or anemia) or risk factors for Barrett's esophagus, endoscopy is strongly recommended as the first step for evaluating esophageal mucosa. In contrast, the Chinese expert consensus recommends endoscopy for all patients with reflux symptoms at the initial diagnosis.[5] The rationale is based on the fact that China is a country with a high incidence of upper gastrointestinal tumors and readily available gastroscopy at a low cost.[6-8] Early endoscopic examination is beneficial for tumor screening and assessment of disease status. A meta-analysis found that the tumor detection rate of endoscopy in patients with upper gastrointestinal symptoms at the initial consultation in Asia was 1.3%.[6] A study in Guangzhou reported a detection rate of 0.8% for esophageal and gastric cancers in patients with initial heartburn without alarm symptoms.[7] However, no study provides economic evidence for this strategy in China. Therefore, we compared the two recommended diagnostic processes described above using a Chinese population-based health economics analysis.

## METHODS

Our analysis considered a hypothetical cohort of patients with typical reflux symptoms (heartburn and regurgitation) in China. Our decision tree model incorporated base-case estimates of most likely clinical scenarios and then used sensitivity analysis to evaluate a range of cost and probability estimates on costs and health outcomes over a one-year time horizon from the health care system perspective. All analyses were performed using TreeAge Pro 2022 software.

### Decision Model

The decision model considered two strategies representing different diagnostic processes in international or Chinese guideline recommendations (Figure 1).

As recommended in international guidelines, the first strategy begins with hazard stratification based on alarm symptoms, including dysphagia, weight loss, gastrointestinal bleeding, and persistent vomiting (stratified endoscopy strategy). Patients without alarm symptoms are considered at low risk of malignancy and receive PPI as diagnostic treatment. Ineffective PPI therapy is indicative of sequential invasive testing utilizing endoscopy and esophageal reflux monitoring. Patients with alarm symptoms directly undergo endoscopic examination, followed by a biopsy for suspected lesions. If no positive endoscopic results are found, a PPI test and esophageal reflux monitoring will be performed for next-step testing. Patients with reflux esophagitis (RE) or Barrett's esophagus (BE) confirmed by endoscopic biopsy, positive PPI response, or reflux evidence from esophageal monitoring are diagnosed as GERD

in this strategy. Peptic ulcer disease (PUD) and upper gastrointestinal carcinoma (CA) can also be detected during endoscopy examination. If endoscopy, PPI test, and reflux monitoring are negative, GERD is excluded.

The second strategy is based on an expert consensus in China, the endoscopy-first strategy. All patients first complete an endoscopic examination. The subsequent assessment algorithm is the same as that in the first strategy.

The biopsy is considered the gold standard for differentiating upper gastrointestinal lesions under endoscopy and esophageal monitoring for pathological reflux. We did not consider the potential side effects of PPI, complications of diagnostic procedures, or the impact of the diagnosis on quality of life or the subsequent utilization of healthcare resources.

**Clinical Inputs and transition probabilities**

Preference was given to the most recent studies based on the Chinese population. When more than one value of the same parameters was reported in multiple studies, the maximum and minimum values, 95% confidence interval, or baseline±20% if insufficient parameters, were included as the value range. For unavailable parameters, data were obtained through expert consultation or referred to relevant studies from other countries. All input parameters are listed in Table 1.

**Disease prevalence.** Bai et al. conducted a large-scale retrospective analysis in a single tertiary medical center and demonstrated the symptomatic profile of patients undergoing upper endoscopy.[9] A total of 15,431 patients had regurgitation or heartburn, and 1,204 had alarm symptoms (7.8%). Common endoscopic lesions included RE, PUD, and BE, while CA was rarely detected. In patients with reflux symptoms but no alarm symptoms, the proportions of RE, PUD, and CA were 25.8%, 12.7%, and 0.7%, respectively.[10] However, no study has separately characterized endoscopic performance in patients with reflux and alarm symptoms. The results from all alarm symptom populations (12.5% RE, 17.9% PUD, and 7.7% CA under endoscopy) were used to estimate these parameters in our model.[10] For all patients with reflux symptoms, the proportions were calculated using the following formula:

*Probability of certain lesion in all patients = Probability of certain lesion in patients with alarm symptoms × Probability of alarm symptoms + Probability of certain lesion in patients without alarm symptoms × (1 - Probability of alarm symptoms)*

The detected rate of BE has been rarely investigated, and the approximate estimation of baseline values was obtained through a meta-analysis (total endoscopic detection rate 1.0%, 95% CI 0.1%-1.8%).[11] The proportion of patients without clinically significant endoscopic findings in this model was calculated from 1 minus the sum of other lesions.

**Diagnostic test characteristics.** The response rate of PPI over 2-8 weeks in patients with reflux symptoms ranged from 54.1% to 63.9%.[12-16] We chose the result of an RCT evaluating esomeprazole as the baseline.[14] The PPI test's pooled sensitivity, specificity, and positive predictive value from a previous meta-analysis were 0.52, 0.32, and 0.38, respectively.[17] Esophageal reflux monitoring was once considered the “gold standard” in many DTAs and guidelines. However, the diagnostic performance in Chinese patients was limited, and results varied widely.[18-21] Wang et al. retrospectively investigated 177 patients with typical reflux symptoms who received esophageal function tests, and 122 of them had AET>4%. In patients who did not respond to PPI, 50.0% had AET>4%. In patients without positive endoscopic findings, 65.9% had AET>4%.[18]

**Cost.** All costs were converted to US dollars using published exchange rates. Only direct healthcare costs were considered. Costs for drugs and endoscopic and diagnostic procedures were referenced in

terms of drug and medical service pricing in Peking Union Medical College Hospital. There was no time discounting of future costs and health outcomes as the period of the model was less than one year.

**Base-case analysis**

The base-case analysis estimated the incremental cost-effectiveness ratio (ICER) between the stratified endoscopy strategy and the endoscopy-first strategy. We used the incremental cost per additional correct diagnosis of GERD. As a primary outcome measure for effectiveness, the correct diagnosis of GERD (including biopsy-confirmed RE and BE, NERD confirmed by reflux monitoring, and true positive results in the PPI test) was assigned a value of 1. When the final diagnosis was incorrect (false positive) or was determined as PUD, CA or other disorders, we assigned a value of 0. We also evaluated the incremental cost per additional detection of upper gastrointestinal CA (biopsy-confirmed CA was assigned a value of 1, while other results were 0). The result of cost-effectiveness analysis was only described in this study since there is no accepted willing-to-pay (WTP) threshold for ICER.

**Sensitivity Analysis**

To evaluate the robustness of the results of the decision tree analyses, we explored broad distributions around uncertain parameters using one-way sensitivity analysis. Each parameter varied within the value range to explore the potential factors affecting the optimal strategy, and the results were shown in the tornado diagrams.

**Patient and Public Involvement**

No patients were involved in the development of the research question or its outcome measures, the conduct of the research, or the preparation of the manuscript.

## RESULTS

**Base case analysis**

The results of our base case analysis are presented in Table 2. The total expected costs were $122.51 for the stratified endoscopy strategy and $150.12 for the endoscopy-first strategy. The rate of correct diagnosis of GERD was 0.45 and 0.52 for the stratified strategy and the endoscopy-first strategy, respectively. The ICER comparing the endoscopy-first strategy with the stratified endoscopy strategy was $440.39 per additional correct case of GERD. The rates of detecting upper gastrointestinal CA of the two strategies were 0.0088 and 0.0120. The ICER was $8561.34. A total of 47.4% of patients underwent endoscopy, and 25.8% finished reflux monitoring in the stratified endoscopy strategy. In the other strategy, where all patients underwent endoscopy, 25.7% needed reflux monitoring.

**One-way sensitivity analyses**

The one-way sensitivity analysis related to the GERD diagnosis is shown in Figure 2. The most sensitive parameters were the probability of RE in patients without alarm symptoms, the probability of true positives in the PPI test, the probability of RE in all patients, the cost of endoscopy, and the probability of patients with alarm symptoms. When the probability of RE in patients without alarm symptoms varied from 0.206 to 0.410, the ICER would range from 324.78 to 1190.42; when the probability of true positives in the PPI test varied from 0.300 to 0.490, the ICER would range from 348.07 to 693.18; when the probability of RE in all patients varied from 0.227 to 0.298, the ICER would range from 580.22 to 254.93; when the cost of endoscopy varied from 45.103 to 67.654, the ICER would range from 345.72

to 535.06; when the probability of patients with alarm symptoms varied from 0.062 to 0.270, the ICER would range from 455.33 to 291.56 (Table S1).

## DISCUSSION

There is an increasing trend of GERD globally, as well as in the Chinese population. However, the diagnostic processes still vary in different regions of the world.[2,4,5] The endoscopy-first strategy used in China was more effective but also more expensive than the stratified endoscopy strategy recommended by international guidelines.

The Chinese expert consensus that prioritizes the recommendation of endoscopy is based on two main facts, the first of which is the risk of malignant lesions.[5] Upper gastrointestinal tract cancer (UGIC), including esophageal cancer (EC) and gastric cancer (GC), is prevalent in China.[29] In 2020, UGIC accounted for 11.38% and 15.97% of all new incidence cases and deaths from malignant tumors in China.[29] Endoscopic screening can reduce the incidence and mortality associated with UGIC.[30-33] Multiple economic evaluation studies from different countries indicated that endoscopic screening was cost-effective compared with no screening.[34-39] Xia et al. constructed a Markov model to evaluate the cost-effectiveness of endoscopic screening strategies for UGIC among people aged 40 to 69 years in areas of China where the risk of these cancers is high.[40] Combined endoscopic screening for EC and GC may be cost-effective, and screening every two years would be optimal. The use of endoscopy is common in China. According to the national gastrointestinal endoscopy census in 2020, from 2012 to 2019, the number of medical institutions conducting gastrointestinal endoscopies increased from 6,128 to 7,470; the number of practitioners had a growth rate of 51.27%, and a total of 38,730,000 cases of gastrointestinal endoscopy were carried out nationwide in 2019, representing an increase of 34.62% from 2012.

When we focused on diagnosing GERD or CA in this model, the endoscopy-first strategy showed increased effectiveness and more costs. The use of alarm symptom stratification avoided endoscopy in more than half of all patients, while the need for expensive reflux monitoring was comparable between the two strategies. Moreover, we noted that the proportion of CA in the reflux symptomatic population does not correlate with the traditionally high prevalence of upper gastrointestinal CA in China. In addition, chronic inflammation caused by GERD is one of the most critical risk factors for esophageal adenocarcinoma, while squamous carcinoma accounts for more than 80% of cases in China.[41] Therefore, the significance of reflux symptoms alone in suggesting upper gastrointestinal malignancies in the Chinese population still needs to be supported by large-scale studies.

According to the one-way sensitivity analysis, the first five factors affecting the baseline results of ICER were the probability of RE in patients without alarm symptoms, the probability of true positives in the PPI test, the probability of RE in all patients, the cost of endoscopy, and the probability of patients with alarm symptoms. Based on the literature search results, alarm symptoms are commonly used exclusion criteria when investigating endoscopic manifestations. RE is the most common lesion observed under endoscopy in patients with reflux symptoms, and the range of its probability was obtained from different single-centered research data covering the provinces of Guangdong, Shanghai, Beijing, and Xinjiang.[7,10,19,24,25] However, given the differences between regions and age groups in China, the characterization of upper digestive tract lesions detected by endoscopy still requires more well-planned epidemiological investigations. For the diagnostic accuracy of the PPI test, pooled results and its 95% confidence interval from a meta-analysis were used as baseline and range.[17] However, these results are not specific to the Chinese population alone. The price of endoscopes is another critical point to focus

on. We used the pricing of endoscopes in Beijing hospitals as the basis, with a 20% upward and downward fluctuation as the range according to expert consultation. The real world is bound to be more complex, influenced by different regions, hospital grades, and health insurance policies. The main difference between the two strategies compared in this decision tree model is risk stratification according to the presence or absence of alarm symptoms. Therefore, the proportion of alarm symptoms in the tested population obviously has a greater impact on the results of the model operation. When the probability of alarm symptoms increased, more subjects directly entered the endoscopy session, and the difference between the two strategies decreased, with the ICER showing a decreasing trend.

In 1999, Ofman et al. compared the clinical and economic outcomes of the empiric trial of omeprazole and the traditional invasive strategy for diagnosing GERD as the cause of non-cardiac chest pain.[42] Results showed that the omeprazole test was related to reduced costs and improved diagnostic certainty, providing a simple, cost-effective choice for common disorders in primary care settings. However, no cost-effectiveness studies compared different diagnosis strategies in patients with typical reflux. Compared to non-cardiac chest pain, reflux symptoms suggest different differential diagnoses and different significance in predicting malignancy, thus affecting patient treatment choices and outcomes. The stratified endoscopy strategy in this model used alarm symptoms as the rationale for hazard stratification. Additional factors are considered to identify high risk for malignant lesions, including region, family history, dietary habits, H. pylori infection, etc, which are potential to be included in further hazard stratification. Accurate risk stratification helps to highlight the value of endoscopy for precise screening and definite diagnosis rather than crude primary screening.

This study had some limitations. One of the significant limitations is the one-year time horizon. The study did not measure the costs and outcomes related to treatment, survival, and disability. Cost-effectiveness was not measured in terms of cost per disability-adjusted life year averted, which is a more robust measure of cost-effectiveness. Moreover, our model is structured based on several assumptions and parameter estimates. Parameter estimates were extracted from multiple sources with different evidence quality. Considering that the prevalence also varies considerably in various regions of China and different periods of age, these results are bound to change with changes in prevalence rates from other populations. More epidemiological findings based on Chinese populations are urgently needed as a basis for further health economic analysis.

## CONCLUSION

This study provides economic evidence for the expert consensus of GERD in China. The use of endoscopy for all patients with reflux symptoms was more effective but with an increased cost compared with the strategy recommended in international guidelines. Diagnosing GERD while ruling out malignant lesions in the vastly outnumbered reflux population in China still requires more targeted, higher-quality endoscopy strategies depending on the regional spectrum of diseases and accessibility of medical resources.

**Figure legends:**

**Figure 1. Decision tree model for cost-effectiveness analysis. □: decision nodes, ○: chance nodes, ▷: terminal nodes;** RE, reflux esophagitis; PUD, peptic ulcer disease; BE, Barrett's esophagus; CA, carcinoma; PPI, proton pump inhibitors; NERD, non-erosive reflux disease; GERD, gastroesophageal reflux disease.

**Figure 2. Tornado diagram of ICER.** RE, reflux esophagitis; PUD, peptic ulcer disease; BE,

Barrett's esophagus; CA, carcinoma; PPI, proton pump inhibitors.

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**Contributors:** XY and DW designed the study. XY, XL, YC, MO, ZG, CL, DY contributed to the conduction of the study. XY and XL collected the data. XY and XL performed statistical analysis and wrote the draft of the manuscript. HC and FX provided advices for the research protocol, statistical analysis plan and data analyses. HC, FX and DW reviewed and edited the manuscript. All authors read and approved the final manuscript. [Dong Wu / DW] is responsible for the overall content as guarantor.

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**Data sharing statement:** This study was based on published data. The data used for analyses are available and shown in table.

**Ethics approval:** This study used a decision tree model based on published data, and no ethics approval and informed consent were requested.

**Competing interests:** All the authors have no conflict of interest to declare.

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**Table 1. Model parameters**

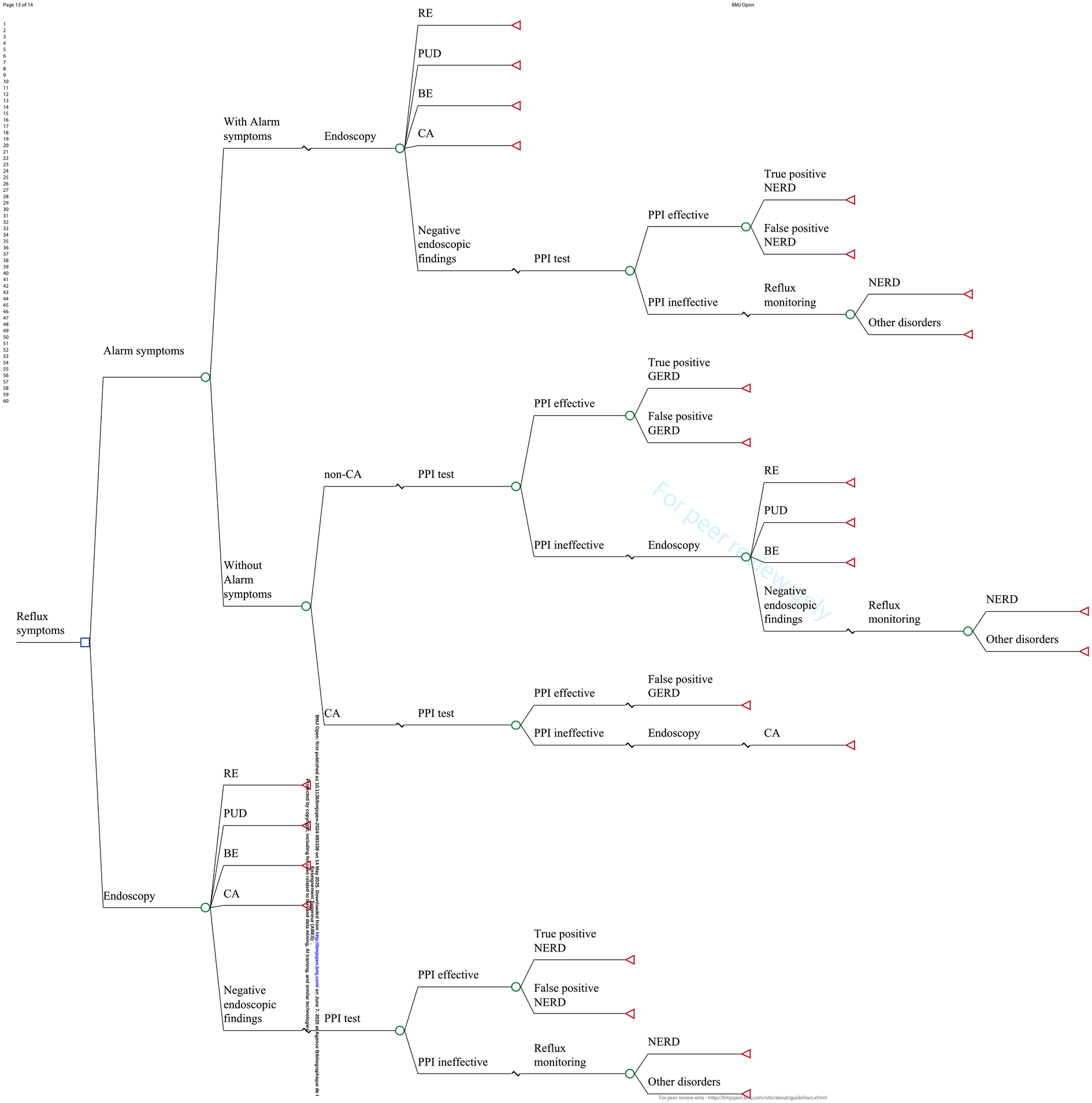
| Parameters | Baseline | Range | Reference |
|---|---|---|---|
| **Clinical probability** | | | |
| Proportion of patients with alarm symptoms | 0.078 | 0.062-0.270 | 9,10,22,23 |
| Response rate to PPI treatment | 0.571 | 0.457-0.685 | 12-16 |
| Probability of true positive in PPI test | 0.380 | 0.300-0.490 | 17 |
| Probability of positive reflux monitoring | 0.500 | 0.400-0.689 | 18,20 |
| **In patients with alarm symptoms** | | | |
| Probability of RE under endoscopy | 0.125 | 0.100-0.359 | 10.23 |
| Probability of PUD under endoscopy | 0.179 | 0.143-0.476 | 10,22,23 |
| Probability of BE under endoscopy | 0.010 | 0.001-0.018 | 11 |
| Probability of CA under endoscopy | 0.077 | 0.023-0.172 | 10,23 |
| **In patients without alarm symptoms** | | | |
| Probability of RE under endoscopy | 0.258 | 0.206-0.410 | 7,10,19,24,25 |
| Probability of PUD under endoscopy | 0.127 | 0.027-0.152 | 7,10,19,24 |
| Probability of BE under endoscopy | 0.010 | 0.001-0.018 | 11 |
| Probability of CA under endoscopy | 0.007 | 0.004-0.009 | 7,10,19,26 |
| **In all patients with reflux symptoms** | | | |
| Probability of RE under endoscopy | 0.248 | 0.227-0.298 | 10,27,28 |
| Probability of PUD under endoscopy | 0.131 | 0.068-0.157 | 10,27 |
| Probability of BE under endoscopy | 0.010 | 0.001-0.018 | 11 |
| Probability of CA under endoscopy | 0.012 | 0.010-0.017 | 10,27 |
| **Cost ($)** | | | |
| Cost of PPI[a] | 28.602 | 22.826-34.377 | |
| Cost of upper endoscopy | 56.378 | 45.103-67.654 | |
| Cost of endoscopic biopsy | 41.253 | 33.002-49.503 | |
| Cost of esophageal reflux monitoring | 233.760 | 187.010-280.520 | |

a. Omeprazole 20mg bid for two weeks. RE, reflux esophagitis; PUD, peptic ulcer disease; BE, Barrett's esophagus; CA, carcinoma; PPI, proton pump inhibitors.

**Table 2. Base-case analysis**

| Strategy | Cost ($) | Diagnosis of GERD | | Detection of CA | |
|---|---|---|---|---|---|
| | | Effectiveness | ICER | Effectiveness | ICER |
| Stratified endoscopy strategy | 122.5103 | 0.4538 | | 0.0088 | |
| Endoscopy-first strategy | 150.1226 | 0.5165 | 440.3854 | 0.0120 | 8561.3360 |

GERD, gastroesophageal reflux disease; CA, carcinoma; ICER, incremental cost-effectiveness ratio.



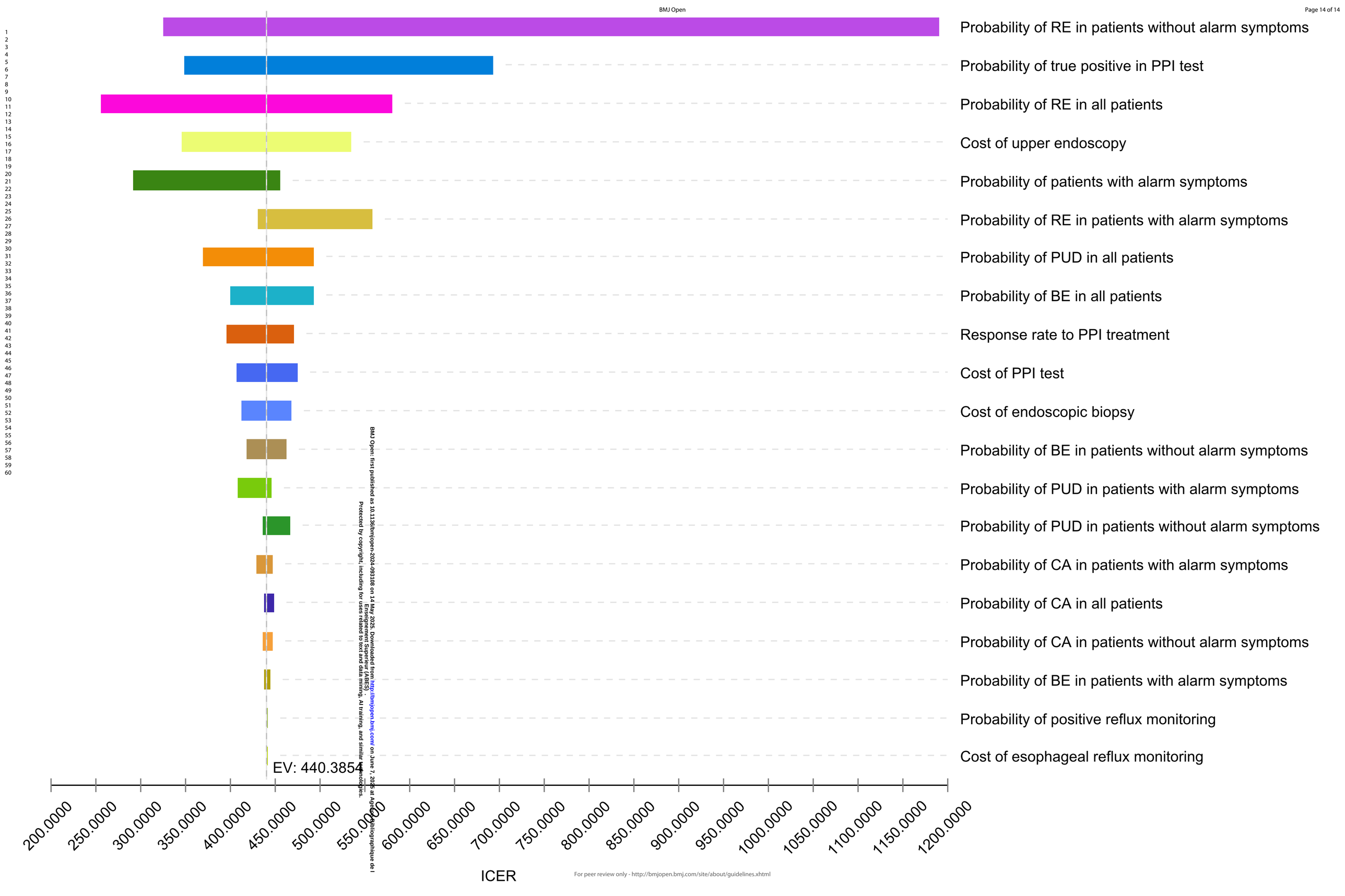


**Table S1: Incremental cost-effectiveness ratios (ICERs) under variations in parameter values**

| Parameters | Minimal value | ICER | Maximal value | ICER |
|---|---|---|---|---|
| **Clinical probability** | | | | |
| Proportion of patients with alarm symptoms | 0.062 | 455.3254 | 0.270 | 291.5560 |
| Response rate to PPI treatment | 0.457 | 394.9669 | 0.685 | 470.8678 |
| Probability of true positive in PPI test | 0.300 | 348.0688 | 0.490 | 693.1761 |
| Probability of positive reflux monitoring | 0.400 | 439.6612 | 0.689 | 441.7606 |
| **In patients with alarm symptoms** | | | | |
| Probability of RE under endoscopy | 0.100 | 430.0561 | 0.359 | 558.2894 |
| Probability of PUD under endoscopy | 0.143 | 445.0610 | 0.476 | 407.7583 |
| Probability of BE under endoscopy | 0.001 | 436.6250 | 0.018 | 443.7683 |
| Probability of CA under endoscopy | 0.023 | 447.4686 | 0.172 | 428.8724 |
| **In patients without alarm symptoms** | | | | |
| Probability of RE under endoscopy | 0.206 | 324.7811 | 0.410 | 1190.4202 |
| Probability of PUD under endoscopy | 0.027 | 465.6376 | 0.152 | 436.3645 |
| Probability of BE under endoscopy | 0.001 | 417.7561 | 0.018 | 461.5989 |
| Probability of CA under endoscopy | 0.004 | 447.2920 | 0.009 | 435.9352 |
| **In all patients with reflux symptoms** | | | | |
| Probability of RE under endoscopy | 0.227 | 580.2160 | 0.298 | 254.9286 |
| Probability of PUD under endoscopy | 0.068 | 368.6227 | 0.157 | 492.0933 |
| Probability of BE under endoscopy | 0.001 | 493.2129 | 0.018 | 400.1763 |
| Probability of CA under endoscopy | 0.010 | 437.1639 | 0.017 | 448.8410 |
| **Cost ($)** | | | | |
| Cost of PPI[a] | 22.826 | 474.5163 | 34.377 | 406.2604 |
| Cost of upper endoscopy | 45.103 | 345.7151 | 67.654 | 535.0641 |
| Cost of endoscopic biopsy | 33.002 | 412.4099 | 49.503 | 468.3575 |
| Cost of esophageal reflux monitoring | 187.010 | 441.1554 | 280.520 | 439.6152 |

a. Omeprazole 20mg bid for two weeks. RE, reflux esophagitis; PUD, peptic ulcer disease; BE, Barrett's esophagus; CA, carcinoma; PPI, proton pump inhibitors; ICER, incremental cost-effectiveness ratio.

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# Health economics evaluation of diagnostic strategies for gastroesophageal reflux disease with reflux symptoms in China: a modelling study

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# Health economics evaluation of diagnostic strategies for gastroesophageal reflux disease with reflux symptoms in China: a modelling study

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## Abstract

**Objectives:** American College of Gastroenterology (ACG) and Chinese expert consensus recommended different algorithmic approaches for the diagnosis of gastroesophageal reflux disease (GERD) are not yet defined. We compared the two recommended diagnostic processes using a Chinese population-based health economics analysis.

**Methods:** Our analysis considered a hypothetical cohort of patients with typical reflux symptoms. We constructed a decision tree model to compare the two recommended diagnostic processes described in ACG clinical guidelines (stratified endoscopy strategy) and Chinese expert consensus (endoscopy-first strategy). The first strategy begins with hazard stratification based on alarm symptoms. Patients with alarm symptoms directly undergo endoscopic examination, while patients without alarm symptoms receive proton pump inhibitor as diagnostic treatment. In the second strategy, all patients with reflux symptoms complete an endoscopic examination. Sensitivity analysis was performed to evaluate a range of cost and probability estimates on costs and health outcomes over a one-year time horizon from the health care system perspective.

**Results:** The total expected costs were $122.51 for the stratified endoscopy strategy and $150.12 for the endoscopy-first strategy. The ICER comparing the endoscopy-first strategy with the stratified endoscopy strategy was $440.39 per additional correct case of GERD. The rates of detecting upper gastrointestinal CA of the two strategies were 0.0088 and 0.0120, and the ICER was $8561.34.

**Conclusions:** The use of endoscopy for all patients with reflux symptoms was more effective but with an increased cost compared with the strategy recommended in international guidelines.


Key Words: Gastroesophageal reflux disease; Endoscopy; Reflux symptom; Cost-effectiveness analysis; Decision tree model

### Strengths and limitations of this study

- ✓ Nationally representative data sources based on a particular population were used.
- ✓ Sensitivity analysis was done to determine the uncertainty in the estimates.
- ✓ Costs and outcomes related to treatment, survival, and disability were not measured.
- ✓ Regional differences among the Chinese population were not considered.

## INTRODUCTION

Gastroesophageal reflux disease (GERD) is a condition in which reflux of gastric contents causes troublesome symptoms and complications. Although heartburn and regurgitation are considered typical symptoms associated with GERD, a broad spectrum of other symptoms include dysphagia, chest pain, painful swallowing, and extraesophageal symptoms (e.g., chronic cough, hoarseness, laryngitis, pharyngitis, and pulmonary fibrosis).[1] The estimated global prevalence of GERD is 13% and varies considerably by region and population. In mainland China, the overall pooled prevalence of GERD was 8.7% and showed an increasing trend.[2,3] Considering the large population size of China, effective screening and management strategies for GERD are needed.

The diagnosis of GERD is commonly based on the combination of symptoms, endoscopic findings, reflux monitoring, and therapeutic response.[1] American College of Gastroenterology (ACG) clinical guidelines recommend starting with a proton pump inhibitor (PPI) among patients with typical symptoms.[4] For patients with alarm symptoms (such as dysphagia, weight loss, bleeding, vomiting, and/or anemia) or risk factors for Barrett's esophagus, endoscopy is strongly recommended as the first step for evaluating esophageal mucosa. In contrast, the Chinese expert consensus recommends endoscopy for all patients with reflux symptoms at the initial diagnosis.[5] The rationale is based on the fact that China is a country with a high incidence of upper gastrointestinal tumors and readily available gastroscopy at a low cost.[6-8] Early endoscopic examination is beneficial for tumor screening and assessment of disease status. A meta-analysis found that the tumor detection rate of endoscopy in patients with upper gastrointestinal symptoms at the initial consultation in Asia was 1.3%.[6] A study in Guangzhou reported a detection rate of 0.8% for esophageal and gastric cancers in patients with initial heartburn without alarm symptoms.[7] However, no study provides economic evidence for this strategy in China. Therefore, we compared the two recommended diagnostic processes described above using a Chinese population-based health economics analysis.

## METHODS

Our analysis considered a hypothetical cohort of patients with typical reflux symptoms (heartburn and regurgitation) in China. Our decision tree model incorporated base-case estimates of most likely clinical scenarios and then used sensitivity analysis to evaluate a range of cost and probability estimates on costs and health outcomes over a one-year time horizon from the health care system perspective. All analyses were performed using TreeAge Pro 2022 software.

### Decision Model

The decision model considered two strategies representing different diagnostic processes in international or Chinese guideline recommendations (Figure 1).

As recommended in international guidelines, the first strategy begins with hazard stratification based on alarm symptoms, including dysphagia, weight loss, gastrointestinal bleeding, and persistent vomiting (stratified endoscopy strategy). Patients without alarm symptoms are considered at low risk of malignancy and receive PPI as diagnostic treatment. Ineffective PPI therapy is indicative of sequential invasive testing utilizing endoscopy and esophageal reflux monitoring. Patients with alarm symptoms directly undergo endoscopic examination, followed by a biopsy for suspected lesions. If no positive endoscopic results are found, a PPI test and esophageal reflux monitoring will be performed for next-step testing. Patients with reflux esophagitis (RE) or Barrett's esophagus (BE) confirmed by endoscopic biopsy, positive PPI response, or reflux evidence from esophageal monitoring are diagnosed as GERD

in this strategy. Peptic ulcer disease (PUD) and upper gastrointestinal carcinoma (CA) can also be detected during endoscopy examination. If endoscopy, PPI test, and reflux monitoring are negative, GERD is excluded.

The second strategy is based on an expert consensus in China, the endoscopy-first strategy. All patients first complete an endoscopic examination. The subsequent assessment algorithm is the same as that in the first strategy.

The biopsy is considered the gold standard for differentiating upper gastrointestinal lesions under endoscopy and esophageal monitoring for pathological reflux. We did not consider the potential side effects of PPI, complications of diagnostic procedures, or the impact of the diagnosis on quality of life or the subsequent utilization of healthcare resources.

**Clinical Inputs and transition probabilities**

Preference was given to the most recent studies based on the Chinese population. When more than one value of the same parameters was reported in multiple studies, the maximum and minimum values, 95% confidence interval, or baseline±20% if insufficient parameters, were included as the value range. For unavailable parameters, data were obtained through expert consultation or referred to relevant studies from other countries. All input parameters are listed in Table 1.

**Disease prevalence.** Bai et al. conducted a large-scale retrospective analysis in a single tertiary medical center and demonstrated the symptomatic profile of patients undergoing upper endoscopy.[9] A total of 15,431 patients had regurgitation or heartburn, and 1,204 had alarm symptoms (7.8%). Common endoscopic lesions included RE, PUD, and BE, while CA was rarely detected. In patients with reflux symptoms but no alarm symptoms, the proportions of RE, PUD, and CA were 25.8%, 12.7%, and 0.7%, respectively.[10] However, no study has separately characterized endoscopic performance in patients with reflux and alarm symptoms. The results from all alarm symptom populations (12.5% RE, 17.9% PUD, and 7.7% CA under endoscopy) were used to estimate these parameters in our model.[10] For all patients with reflux symptoms, the proportions were calculated using the following formula:

*Probability of certain lesion in all patients = Probability of certain lesion in patients with alarm symptoms × Probability of alarm symptoms + Probability of certain lesion in patients without alarm symptoms × (1 - Probability of alarm symptoms)*

The detected rate of BE has been rarely investigated, and the approximate estimation of baseline values was obtained through a meta-analysis (total endoscopic detection rate 1.0%, 95% CI 0.1%-1.8%).[11] The proportion of patients without clinically significant endoscopic findings in this model was calculated from 1 minus the sum of other lesions.

**Diagnostic test characteristics.** The response rate of PPI over 2-8 weeks in patients with reflux symptoms ranged from 54.1% to 63.9%.[12-16] We chose the result of an RCT evaluating esomeprazole as the baseline.[14] The PPI test's pooled sensitivity, specificity, and positive predictive value from a previous meta-analysis were 0.52, 0.32, and 0.38, respectively.[17] Esophageal reflux monitoring was once considered the “gold standard” in many DTAs and guidelines. However, the diagnostic performance in Chinese patients was limited, and results varied widely.[18-21] Wang et al. retrospectively investigated 177 patients with typical reflux symptoms who received esophageal function tests, and 122 of them had AET>4%. In patients who did not respond to PPI, 50.0% had AET>4%. In patients without positive endoscopic findings, 65.9% had AET>4%.[18]

**Cost.** All costs were converted to US dollars using published exchange rates. Only direct healthcare costs were considered. Costs for drugs and endoscopic and diagnostic procedures were referenced in

terms of drug and medical service pricing in Peking Union Medical College Hospital. There was no time discounting of future costs and health outcomes as the period of the model was less than one year.

**Base-case analysis**

The base-case analysis estimated the incremental cost-effectiveness ratio (ICER) between the stratified endoscopy strategy and the endoscopy-first strategy. We used the incremental cost per additional correct diagnosis of GERD. As a primary outcome measure for effectiveness, the correct diagnosis of GERD (including biopsy-confirmed RE and BE, NERD confirmed by reflux monitoring, and true positive results in the PPI test) was assigned a value of 1. When the final diagnosis was incorrect (false positive) or was determined as PUD, CA or other disorders, we assigned a value of 0. We also evaluated the incremental cost per additional detection of upper gastrointestinal CA (biopsy-confirmed CA was assigned a value of 1, while other results were 0). The result of cost-effectiveness analysis was only described in this study since there is no accepted willing-to-pay (WTP) threshold for ICER.

**Sensitivity Analysis**

To evaluate the robustness of the results of the decision tree analyses, we explored broad distributions around uncertain parameters using one-way sensitivity analysis. Each parameter varied within the value range to explore the potential factors affecting the optimal strategy, and the results were shown in the tornado diagrams.

**Patient and Public Involvement**

No patients were involved in the development of the research question or its outcome measures, the conduct of the research, or the preparation of the manuscript.

## RESULTS

**Base case analysis**

The results of our base case analysis are presented in Table 2. The total expected costs were $122.51 for the stratified endoscopy strategy and $150.12 for the endoscopy-first strategy. The rate of correct diagnosis of GERD was 0.45 and 0.52 for the stratified strategy and the endoscopy-first strategy, respectively. The ICER comparing the endoscopy-first strategy with the stratified endoscopy strategy was $440.39 per additional correct case of GERD. The rates of detecting upper gastrointestinal CA of the two strategies were 0.0088 and 0.0120. The ICER was $8561.34. A total of 47.4% of patients underwent endoscopy, and 25.8% finished reflux monitoring in the stratified endoscopy strategy. In the other strategy, where all patients underwent endoscopy, 25.7% needed reflux monitoring.

**One-way sensitivity analyses**

The one-way sensitivity analysis related to the GERD diagnosis is shown in Figure 2. The most sensitive parameters were the probability of RE in patients without alarm symptoms, the probability of true positives in the PPI test, the probability of RE in all patients, the cost of endoscopy, and the probability of patients with alarm symptoms. When the probability of RE in patients without alarm symptoms varied from 0.206 to 0.410, the ICER would range from 324.78 to 1190.42; when the probability of true positives in the PPI test varied from 0.300 to 0.490, the ICER would range from 348.07 to 693.18; when the probability of RE in all patients varied from 0.227 to 0.298, the ICER would range from 580.22 to 254.93; when the cost of endoscopy varied from 45.103 to 67.654, the ICER would range from 345.72

to 535.06; when the probability of patients with alarm symptoms varied from 0.062 to 0.270, the ICER would range from 455.33 to 291.56 (Table S1).

## DISCUSSION

There is an increasing trend of GERD globally, as well as in the Chinese population. However, the diagnostic processes still vary in different regions of the world.[2,4,5] The endoscopy-first strategy used in China was more effective but also more expensive than the stratified endoscopy strategy recommended by international guidelines.

The Chinese expert consensus that prioritizes the recommendation of endoscopy is based on two main facts, the first of which is the risk of malignant lesions.[5] Upper gastrointestinal tract cancer (UGIC), including esophageal cancer (EC) and gastric cancer (GC), is prevalent in China.[29] In 2020, UGIC accounted for 11.38% and 15.97% of all new incidence cases and deaths from malignant tumors in China.[29] Endoscopic screening can reduce the incidence and mortality associated with UGIC.[30-33] Multiple economic evaluation studies from different countries indicated that endoscopic screening was cost-effective compared with no screening.[34-39] Xia et al. constructed a Markov model to evaluate the cost-effectiveness of endoscopic screening strategies for UGIC among people aged 40 to 69 years in areas of China where the risk of these cancers is high.[40] Combined endoscopic screening for EC and GC may be cost-effective, and screening every two years would be optimal. The use of endoscopy is common in China. According to the national gastrointestinal endoscopy census in 2020, from 2012 to 2019, the number of medical institutions conducting gastrointestinal endoscopies increased from 6,128 to 7,470; the number of practitioners had a growth rate of 51.27%, and a total of 38,730,000 cases of gastrointestinal endoscopy were carried out nationwide in 2019, representing an increase of 34.62% from 2012.

When we focused on diagnosing GERD or CA in this model, the endoscopy-first strategy showed increased effectiveness and more costs. The use of alarm symptom stratification avoided endoscopy in more than half of all patients, while the need for expensive reflux monitoring was comparable between the two strategies. Moreover, we noted that the proportion of CA in the reflux symptomatic population does not correlate with the traditionally high prevalence of upper gastrointestinal CA in China. In addition, chronic inflammation caused by GERD is one of the most critical risk factors for esophageal adenocarcinoma, while squamous carcinoma accounts for more than 80% of cases in China.[41] Therefore, the significance of reflux symptoms alone in suggesting upper gastrointestinal malignancies in the Chinese population still needs to be supported by large-scale studies.

According to the one-way sensitivity analysis, the first five factors affecting the baseline results of ICER were the probability of RE in patients without alarm symptoms, the probability of true positives in the PPI test, the probability of RE in all patients, the cost of endoscopy, and the probability of patients with alarm symptoms. Based on the literature search results, alarm symptoms are commonly used exclusion criteria when investigating endoscopic manifestations. RE is the most common lesion observed under endoscopy in patients with reflux symptoms, and the range of its probability was obtained from different single-centered research data covering the provinces of Guangdong, Shanghai, Beijing, and Xinjiang.[7,10,19,24,25] However, given the differences between regions and age groups in China, the characterization of upper digestive tract lesions detected by endoscopy still requires more well-planned epidemiological investigations. For the diagnostic accuracy of the PPI test, pooled results and its 95% confidence interval from a meta-analysis were used as baseline and range.[17] However, these results are not specific to the Chinese population alone. The price of endoscopes is another critical point to focus

on. We used the pricing of endoscopes in Beijing hospitals as the basis, with a 20% upward and downward fluctuation as the range according to expert consultation. The real world is bound to be more complex, influenced by different regions, hospital grades, and health insurance policies. The main difference between the two strategies compared in this decision tree model is risk stratification according to the presence or absence of alarm symptoms. Therefore, the proportion of alarm symptoms in the tested population obviously has a greater impact on the results of the model operation. When the probability of alarm symptoms increased, more subjects directly entered the endoscopy session, and the difference between the two strategies decreased, with the ICER showing a decreasing trend. The probabilistic sensitivity analysis would provide a more comprehensive understanding of the uncertainty in our model. However, due to the lack of a recognized WTP threshold, we are unable to conduct a probabilistic sensitivity analysis at this stage. Although the one-way sensitivity analyses may not capture the full range of uncertainty, we believe it offers preliminary insights and highlights potential directions for future research. We hope that as more data and methodological support become available, probabilistic sensitivity analysis can be incorporated in subsequent studies.

In 1999, Ofman et al. compared the clinical and economic outcomes of the empiric trial of omeprazole and the traditional invasive strategy for diagnosing GERD as the cause of non-cardiac chest pain.[42] Results showed that the omeprazole test was related to reduced costs and improved diagnostic certainty, providing a simple, cost-effective choice for common disorders in primary care settings. However, no cost-effectiveness studies compared different diagnosis strategies in patients with typical reflux. Compared to non-cardiac chest pain, reflux symptoms suggest different differential diagnoses and different significance in predicting malignancy, thus affecting patient treatment choices and outcomes. The stratified endoscopy strategy in this model used alarm symptoms as the rationale for hazard stratification. Additional factors are considered to identify high risk for malignant lesions, including region, family history, dietary habits, H. pylori infection, etc, which are potential to be included in further hazard stratification. Accurate risk stratification helps to highlight the value of endoscopy for precise screening and definite diagnosis rather than crude primary screening.

This study had some limitations. One of the significant limitations is the one-year time horizon. The study did not measure the costs and outcomes related to treatment, survival, and disability. Cost-effectiveness was not measured in terms of cost per disability-adjusted life year averted, which is a more robust measure of cost-effectiveness. Moreover, our model is structured based on several assumptions and parameter estimates. Parameter estimates were extracted from multiple sources with different evidence quality. Considering that the prevalence also varies considerably in various regions of China and different periods of age, these results are bound to change with changes in prevalence rates from other populations. More epidemiological findings based on Chinese populations are urgently needed as a basis for further health economic analysis. While our decision tree model offers a systematic approach for selecting GERD diagnostic strategies, it is important to acknowledge that this remains a model-based study. Potential gaps may exist between the theoretical framework and real-world clinical practice, including variations in patient populations, healthcare settings, and resource availability. Future studies should aim to validate and refine this model using large-scale, real-world data to assess its practicality and generalizability. Such efforts would strengthen the evidence base for optimal strategy selection and provide more robust recommendations tailored to diverse clinical scenarios.

## CONCLUSION

This study provides economic evidence for the expert consensus of GERD in China. The use of

endoscopy for all patients with reflux symptoms was more effective but with an increased cost compared with the strategy recommended in international guidelines. Diagnosing GERD while ruling out malignant lesions in the vastly outnumbered reflux population in China still requires more targeted, higher-quality endoscopy strategies depending on the regional spectrum of diseases and accessibility of medical resources.

**Figure legends:**

**Figure 1. Decision tree model for cost-effectiveness analysis. □: decision nodes, ○: chance nodes, ▷: terminal nodes;** RE, reflux esophagitis; PUD, peptic ulcer disease; BE, Barrett's esophagus; CA, carcinoma; PPI, proton pump inhibitors; NERD, non-erosive reflux disease; GERD, gastroesophageal reflux disease.

**Figure 2. Tornado diagram of ICER.** RE, reflux esophagitis; PUD, peptic ulcer disease; BE, Barrett's esophagus; CA, carcinoma; PPI, proton pump inhibitors.

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**Contributors:** XY and DW designed the study. XY, XL, YC, MO, ZG, CL, DY contributed to the conduction of the study. XY and XL collected the data. XY and XL performed statistical analysis and wrote the draft of the manuscript. HC and FX provided advices for the research protocol, statistical analysis plan and data analyses. HC, FX and DW reviewed and edited the manuscript. All authors read and approved the final manuscript. [Dong Wu / DW] is responsible for the overall content as guarantor.

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**Data sharing statement:** This study was based on published data. The data used for analyses are available and shown in table.

**Ethics approval:** This study used a decision tree model based on published data, and no ethics approval and informed consent were requested.

**Competing interests:** All the authors have no conflict of interest to declare.

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**Table 1. Model parameters**

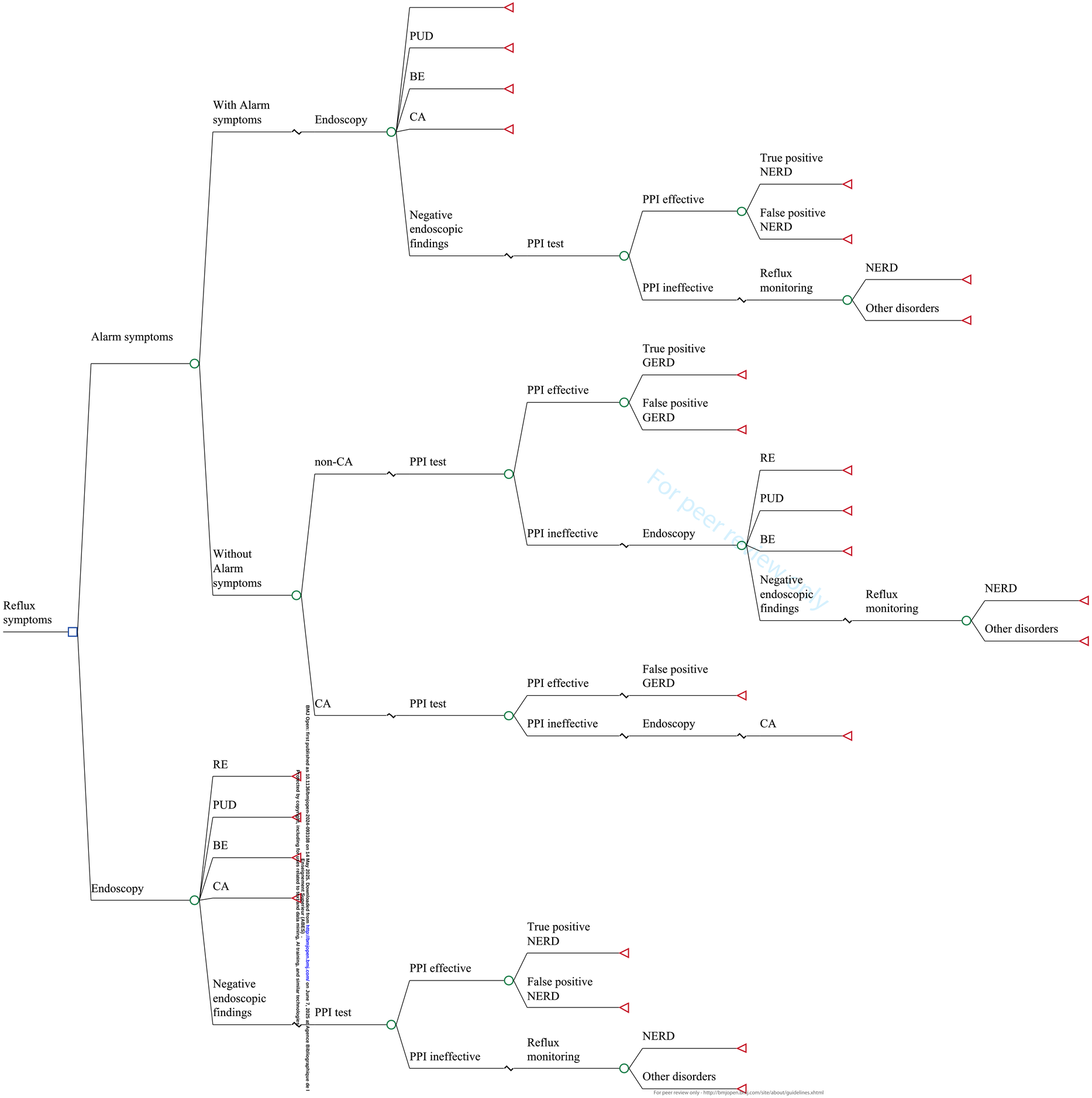
| Parameters | Baseline | Range | Reference |
|---|---|---|---|
| **Clinical probability** | | | |
| Proportion of patients with alarm symptoms | 0.078 | 0.062-0.270 | 9,10,22,23 |
| Response rate to PPI treatment | 0.571 | 0.457-0.685 | 12-16 |
| Probability of true positive in PPI test | 0.380 | 0.300-0.490 | 17 |
| Probability of positive reflux monitoring | 0.500 | 0.400-0.689 | 18,20 |
| **In patients with alarm symptoms** | | | |
| Probability of RE under endoscopy | 0.125 | 0.100-0.359 | 10.23 |
| Probability of PUD under endoscopy | 0.179 | 0.143-0.476 | 10,22,23 |
| Probability of BE under endoscopy | 0.010 | 0.001-0.018 | 11 |
| Probability of CA under endoscopy | 0.077 | 0.023-0.172 | 10,23 |
| **In patients without alarm symptoms** | | | |
| Probability of RE under endoscopy | 0.258 | 0.206-0.410 | 7,10,19,24,25 |
| Probability of PUD under endoscopy | 0.127 | 0.027-0.152 | 7,10,19,24 |
| Probability of BE under endoscopy | 0.010 | 0.001-0.018 | 11 |
| Probability of CA under endoscopy | 0.007 | 0.004-0.009 | 7,10,19,26 |
| **In all patients with reflux symptoms** | | | |
| Probability of RE under endoscopy | 0.248 | 0.227-0.298 | 10,27,28 |
| Probability of PUD under endoscopy | 0.131 | 0.068-0.157 | 10,27 |
| Probability of BE under endoscopy | 0.010 | 0.001-0.018 | 11 |
| Probability of CA under endoscopy | 0.012 | 0.010-0.017 | 10,27 |
| **Cost ($)** | | | |
| Cost of PPI[a] | 28.602 | 22.826-34.377 | |
| Cost of upper endoscopy | 56.378 | 45.103-67.654 | |
| Cost of endoscopic biopsy | 41.253 | 33.002-49.503 | |
| Cost of esophageal reflux monitoring | 233.760 | 187.010-280.520 | |

a. Omeprazole 20mg bid for two weeks. RE, reflux esophagitis; PUD, peptic ulcer disease; BE, Barrett's esophagus; CA, carcinoma; PPI, proton pump inhibitors.

**Table 2. Base-case analysis**

| Strategy | Cost ($) | Diagnosis of GERD | | Detection of CA | |
|---|---|---|---|---|---|
| | | Effectiveness | ICER | Effectiveness | ICER |
| Stratified endoscopy strategy | 122.5103 | 0.4538 | | 0.0088 | |
| Endoscopy-first strategy | 150.1226 | 0.5165 | 440.3854 | 0.0120 | 8561.3360 |

GERD, gastroesophageal reflux disease; CA, carcinoma; ICER, incremental cost-effectiveness ratio.



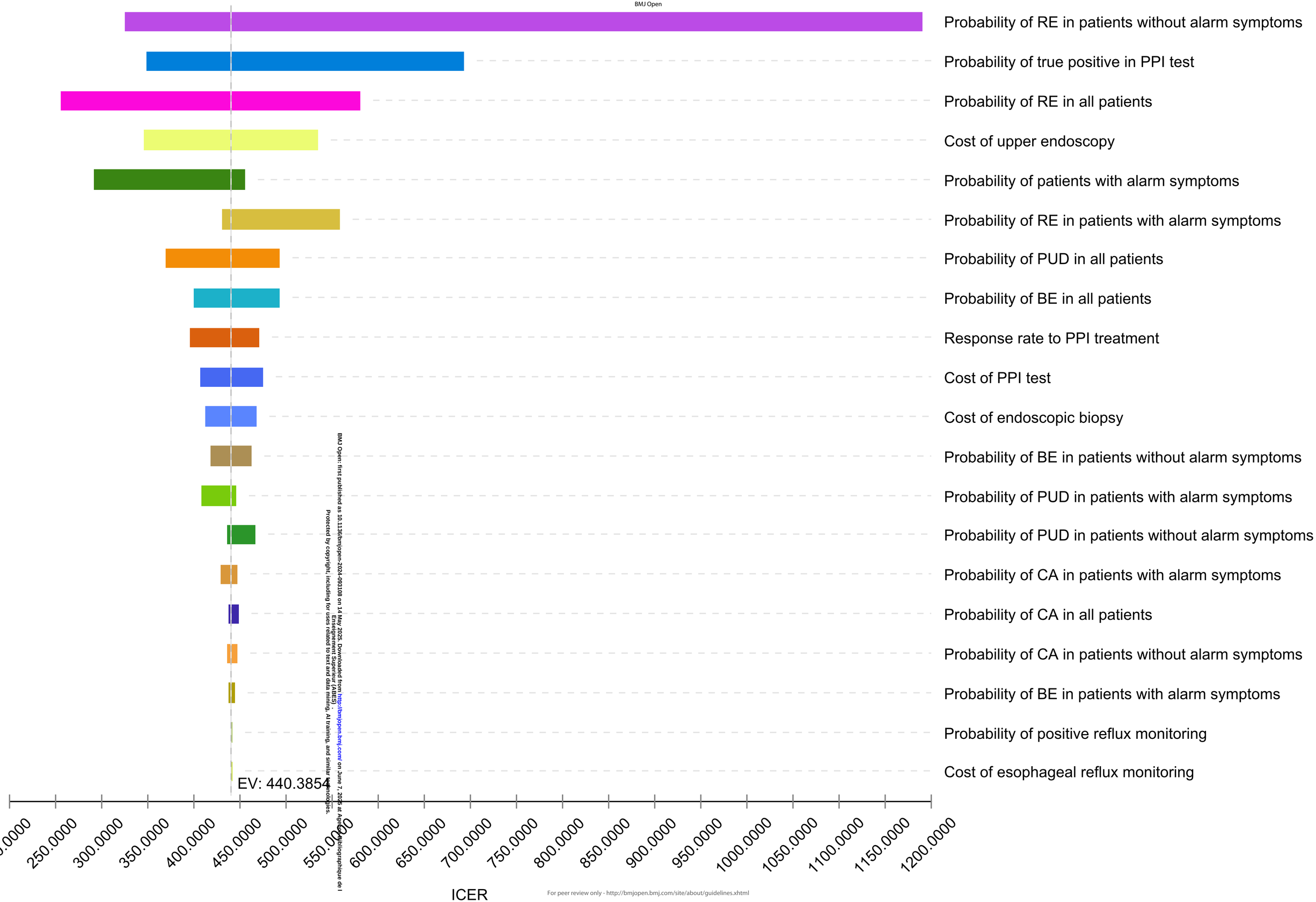


**Table S1: Incremental cost-effectiveness ratios (ICERs) under variations in parameter values**

| Parameters | Minimal value | ICER | Maximal value | ICER |
|---|---|---|---|---|
| **Clinical probability** | | | | |
| Proportion of patients with alarm symptoms | 0.062 | 455.3254 | 0.270 | 291.5560 |
| Response rate to PPI treatment | 0.457 | 394.9669 | 0.685 | 470.8678 |
| Probability of true positive in PPI test | 0.300 | 348.0688 | 0.490 | 693.1761 |
| Probability of positive reflux monitoring | 0.400 | 439.6612 | 0.689 | 441.7606 |
| **In patients with alarm symptoms** | | | | |
| Probability of RE under endoscopy | 0.100 | 430.0561 | 0.359 | 558.2894 |
| Probability of PUD under endoscopy | 0.143 | 445.0610 | 0.476 | 407.7583 |
| Probability of BE under endoscopy | 0.001 | 436.6250 | 0.018 | 443.7683 |
| Probability of CA under endoscopy | 0.023 | 447.4686 | 0.172 | 428.8724 |
| **In patients without alarm symptoms** | | | | |
| Probability of RE under endoscopy | 0.206 | 324.7811 | 0.410 | 1190.4202 |
| Probability of PUD under endoscopy | 0.027 | 465.6376 | 0.152 | 436.3645 |
| Probability of BE under endoscopy | 0.001 | 417.7561 | 0.018 | 461.5989 |
| Probability of CA under endoscopy | 0.004 | 447.2920 | 0.009 | 435.9352 |
| **In all patients with reflux symptoms** | | | | |
| Probability of RE under endoscopy | 0.227 | 580.2160 | 0.298 | 254.9286 |
| Probability of PUD under endoscopy | 0.068 | 368.6227 | 0.157 | 492.0933 |
| Probability of BE under endoscopy | 0.001 | 493.2129 | 0.018 | 400.1763 |
| Probability of CA under endoscopy | 0.010 | 437.1639 | 0.017 | 448.8410 |
| **Cost ($)** | | | | |
| Cost of PPI[a] | 22.826 | 474.5163 | 34.377 | 406.2604 |
| Cost of upper endoscopy | 45.103 | 345.7151 | 67.654 | 535.0641 |
| Cost of endoscopic biopsy | 33.002 | 412.4099 | 49.503 | 468.3575 |
| Cost of esophageal reflux monitoring | 187.010 | 441.1554 | 280.520 | 439.6152 |

a. Omeprazole 20mg bid for two weeks. RE, reflux esophagitis; PUD, peptic ulcer disease; BE, Barrett's esophagus; CA, carcinoma; PPI, proton pump inhibitors; ICER, incremental cost-effectiveness ratio.