Cost-effectiveness analysis of initial nonoperative management versus emergency laparoscopic appendectomy for acute complicated appendicitis in Japan

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Abstract

Background: Although evidence regarding the safety and efficacy of nonoperative management is growing, the best treatment strategy for acute complicated appendicitis remains controversial. In this study, we performed a cost-effectiveness analysis of operative management with emergency laparoscopic appendectomy (ELA) alone as the first-line therapy in complicated appendicitis patients in a municipal hospital in Japan.

Methods: We constructed a Markov model to compare treatment strategies for complicated appendicitis with emergency laparoscopic appendectomy in otherwise-healthy adults. Health outcomes were measured in quality-adjusted life years (QALYs) gained, and cost-effectiveness was evaluated using an incremental cost effectiveness ratio (ICER). Model variables were abstracted from a literature review, and from data from the hospital records of Tochigi Medical Center. Uncertainty surrounding model parameters was assessed via one-way- and probabilistic-sensitivity analyses. Threshold analysis was performed using the willingness-to-pay threshold set at the World Health Organization's criterion of ¥12 million.

Results: Operative management cost ¥677,570 per patient. Nonoperative management without interval laparoscopic appendectomy (ILA) cost ¥109,257 more than operative management and produced only 0.005 more QALYs. Nonoperative management without ILA cost ¥26,049 more than operative management, and also yielded only 0.005 additional QALYs. The ICER for both nonoperative managements were > ¥12 million/QALY in the probabilistic sensitivity analysis.

Conclusions : Nonoperative management with ILA and Nonoperative management without ILA were not cost-effective strategies compared with operative management to treat complicated appendicitis. Operative management remains the standard of care, but nonoperative management deserves serious consideration as a treatment option in complicated appendicitis.

Introduction

Appendicitis is one of the most common acute abdominal diseases and emergency surgeries [1]. Appendectomy is the treatment of choice, and laparoscopic appendectomy has become more common [2] [3]. However, management of patients whose appendicitis is complicated by perforation, cellulitis, or abscess remains controversial.

Patients with complicated appendicitis undergoing immediate surgery might require larger colonic resection and have higher complication risk and longer hospital stay [4] [5] [6]. Therefore, these patients can be treated with antibiotics with image-guided drainage, as needed, without surgery, in the acute setting. This initial nonoperative management is safe, and planning an interval appendectomy in patients with complicated appendicitis appears successful [7] [8]. However, it is also questionable whether such conservative measures should be followed by elective interval appendectomy. A meta-analysis of 61 studies concluded that interval appendectomy may not be necessary in patients who respond to

nonoperative management because the pooled risk of recurrent appendicitis was < 10%, and the incidence of malignancy was < 2% [9].

Therefore, in Japan, there is ongoing debate over the management of complicated appendicitis, and clinicians continue to use both operative and nonoperative treatment strategies. For comparison of competing management strategies in the setting of clinical complexity, the cost-effectiveness analysis is particularly useful to assess which treatment strategy is more effective relation to its cost. To date, and to our knowledge, no study has examined the cost effectiveness of treatment strategies in patients with complicated appendicitis in Japan. Using the technique, we performed a cost-effectiveness analysis of operative management with emergency laparoscopic appendectomy (ELA) alone as the first-line therapy in patients with complicated appendicitis in a municipal hospital in Japan.

Materials And Method

Reference case. For our analysis, the reference case was an adult diagnosed with complicated appendicitis with confirmatory abdominal imaging. The patient was > 18 years of age without comorbidities that would substantially increase their risk of complications from laparoscopic appendectomy and image-guided drainage. Complicated appendicitis was defined as appendiceal inflammation with the presence of appendiceal abscess, cellulitis, or extraluminal air on initial abdominal computed tomographic images.

Treatment Strategies. We compared the cost-effectiveness of the three following treatment strategies from the perspective of health-care payers in Japan (patients, health insurers, and the government): (1) operative management with elective ELA, (2) initial nonoperative management with interval laparoscopic appendectomy (ILA) at 2 months, and (3) nonoperative management without ILA. Nonoperative management entailed hospitalization for 5 days with intravenous cefmetazole as a 3-day course of antibiotics. Computed tomography-guided percutaneous abscess drainage was performed if necessary. All nonoperative treatment failures regardless of the specific indication (e.g., failure to improve, worsening vital signs or laboratory parameters, provider or patient preference) required delayed laparoscopic appendectomy in the same hospitalization. Failures occurring after discharge were considered recurrent appendicitis, and patients with recurrent appendicitis underwent ELA.

Decision model. For the analysis, we used decision analytical modeling using a Markov model to simulate costs, health outcomes, and cost savings while comparing the three treatment strategies (Fig. 1). Given that patients' health states generally return to baseline within 1 year after acute appendicitis, we chose to condense our model by applying the total long-term risk of recurrent appendicitis after nonoperative management into a single year; [12] therefore, we did not include background mortality in the simulation. Each cycle was defined as 1 month in length. The decision model was constructed and analyzed using R, version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

Probabilities

Probabilities of clinical events were abstracted from a literature review (Table 1). [4] [13] [14] The literature review was performed using the PubMed database, using the terms, "Acute appendicitis," "Nonoperative," "Conservative," "Nonsurgical," "Appendectomy," "Complicated," "Abscess," "Perforated," and "Phlegmon." These terms and their combinations were also searched as text words. The search was performed on 5 November 2018, and English language restriction was applied. Because there was limited evidence of the efficacy of laparoscopic appendectomy compared with nonoperative management in treating complicated appendicitis, the inclusion criteria were randomized clinical trials and meta-analyses comparing nonoperative management and operative management (which includes laparoscopic appendectomy) in complicated appendicitis. Exclusion criteria were narrative reviews, studies without control groups, case reports, case series studies, and studies involving pediatric patients.

Costs. Costs were estimated from the health care-payer's perspective; therefore, only direct medical costs were included. The cost of laparoscopic appendectomy in Japan is an unexplored field, and careful attention should be paid to the costing methodology because there is no gold standard. Therefore, for cost analysis, we used a micro-costing method in which the actual monetary health care costs are categorized within the main category: Diagnostic procedures, drugs, ward care, and operating room cost. [15] [16] Data for health care costs were based on the diagnosis-procedure combination/per-diem payment system and fee-for-service, and specific material expenses between 01 April 2011 and 31 March 2018 were retrospectively obtained from the electronic database of the Tochigi Medical Center (Table 2). Costs of perioperative complications were estimated by the increase in average hospitalization cost for complicated appendicitis with complication or comorbidity based on data from our hospital records. We assumed that the costs for outpatient follow-up after hospitalization were equivalent between treatment groups, so these costs were not included in this analysis.

Health-related utility. The primary measures of effectiveness in the present analysis were quality-adjusted life years (QALY) gained. To estimate total QALYs in the Markov model, QALYs were calculated by multiplying the health care-related quality of life (HRQoL) score of a disease state by the duration of time a patient spent in that disease state. We obtained the HRQoL factors from our literature review, and data are shown in Table 3. [12] [17] [18] [19] Because there were few quality-of-life estimates in the literature for the health states of appendicitis, [20] [21] [22] we used the method proposed by Wu et al, in which the utility of undergoing various treatments for appendicitis is estimated by multiplying established utilities by the average duration of hospitalization and recovery from complicated appendicitis associated with each therapeutic strategy [17] [18] [19].

Cost-effectiveness analysis

Cost-effectiveness was evaluated using the incremental cost-effectiveness ratio (ICER). In this analysis, we defined the willingness-to-pay (WTP) threshold based on the criterion of the World Health Organization that states that an intervention is considered cost-effective if the ICER for QALY is 1–3-fold the gross domestic product per capita, [23] which supports the ¥12 million per QALY threshold for cost effectiveness used in this study. Based on this standard, we defined the preferred strategy as the strategy

that produced the greater utility without exceeding a threshold of ¥12 million per QALY. A strategy is considered dominant if it is both less costly and more effective than the reference strategy. Operative management, the current standard of care, was used as the reference group for all comparisons.

Sensitivity analysis

We performed several sensitivity analyses to evaluate the uncertainty and robustness of the model. For these sensitivity analyses, we selected the parameters that covered all potential areas of uncertainty, such as the probabilities, clinical costs, and health-related utility values. One-way sensitivity analyses assessed the effects of varying key model parameters on the ICER. The variation ranges were established based on the analyzed studies. For costs, we allowed values to vary by ± 50% of the index value; variations in sensitivity analysis results are listed in Tables 1–3. We also performed a probabilistic sensitivity analysis to assess the impact of sensitivity on the model parameters using a Monte Carlo simulation with 1000 samples. For the probabilistic sensitivity analysis, all model variables (probabilities, costs, utilities) were set as static with triangular frequency distributions. Additionally, a threshold analysis was performed to determine the cost-effective price of each treatment strategy.

Ethics

This study was approved by the local Ethics Committee on December 3rd, 2018 (number 2018110501).

Results

Cost-effectiveness analysis

Compared with operative management, results showed that nonoperative management with ILA cost ¥109,257 more and yielded 0.005393 additional QALYs, resulting in an ICER of ¥20,259,708 per QALY. Similarly, Nonoperative management without ILA cost ¥26,049 more than operative management and yielded 0.00521 additional QALYs, resulting in an ICER of ¥4,999,809 per QALY. Table 4 shows the estimated ICER for the cohort.

Sensitivity analysis

The tornado diagram (Fig. 2) graphically and simultaneously displays the one-way sensitivity analysis of some of the parameters. Because of the high number of parameters in our analysis, only key parameters in the ICER threshold are shown in the tornado diagram. In nonoperative management with ILA, the parameter with the greatest influence on ICER was the rate of perioperative complications after ELA for complicated appendicitis. One-way sensitivity analysis revealed that nonoperative management with ILA was the preferred strategy compared with operative management if the rate of perioperative complications after ELA for complicated appendicitis was approximately 20%. In nonoperative management without ILA, HRQoL factors related to ELA with preoperative complications had the greatest influence on ICER. If HRQoL factors related to ELA with preoperative complications improved, nonoperative management without ILA was dominated by operative management. Additionally, the

tornado diagram demonstrates a prominent variation in ICER for nonoperative management without ILA. If HRQoL factors related to ELA with preoperative complications increased from 0.245 to 0.995, the ICER of nonoperative management without ILA compared with operative management increased up to ¥600,000,000.

Monte Carlo probabilistic sensitivity analysis showed average ICERs of ¥19,251,676 per QALY for nonoperative management with ILA and ¥50,755,818 per QALY for NOM without ILA, both of which were above the threshold of ¥12,000,000 (Table 5). Our results demonstrated that nonoperative management with ILA was a consistently more effective and more costly strategy compared with operative management. Consistent with the results of the one-way sensitivity analysis, nonoperative management without ILA showed marked variation in cost and effect. Contrary to the results for the reference case, nonoperative management without ILA was not always the preferred strategy compared with operative management in the 1000 simulated cases (Fig. 3).

Uncertainty regarding the cost-effectiveness results also appeared in the cost-effectiveness acceptability curve seen in Figure 4. The curve shows the probability that nonoperative management with ILA and nonoperative management without ILA would be cost-effective with increasing WTP values. We showed that from a WTP of ¥19,251,676 per QALY, the probability is that nonoperative management with ILA would be more cost-effective than operative management. When the WTP threshold reached its maximum value of ¥50,000,000, this probability was approximately 80%. In contrast, regardless of WTP, the possibility that nonoperative management without ILA was the most cost-effective strategy was < 20%.

Discussion

In our analysis, neither nonoperative management with ILA nor nonoperative management without ILA were dominant strategies in the treatment of complicated appendicitis compared with operative management. Base case results demonstrated that nonoperative management without ILA was the most cost-effective and preferred strategy compared with operative management. However, sensitivity analysis showed that nonoperative management without ILA was not a cost-effective strategy among the simulated cases. In contrast, nonoperative management with ILA was the most effective strategy, but also the most costly. Given these findings, we suggest that operative management remains the standard therapeutic strategy, and nonoperative management without ILA and nonoperative management with ILA should not be recommended routinely in the management of complicated appendicitis. To our knowledge, ours is the first study performing an economic analysis comparing the costs of different treatment strategies for complicated appendicitis in the Japanese public health-care system.

Acute appendicitis was complicated by perforation, abscess, or cellulitis in 14.2%–17.8% of cases. [4] [24] However, management of patients diagnosed with complicated appendicitis is still controversial. Immediate surgical treatment of complicated appendicitis is associated with a more than 3-fold increase in morbidity compared with nonoperative management, and may result in unnecessary ileocecal

resection or right-sided hemicolectomy, for technical reasons. [4] Laparoscopic appendectomy offers superior benefits to open appendectomy, and laparoscopic appendectomy has been used for various types of appendicitis. [25] [26] [27] However, the controversy between laparoscopic appendectomy and open appendectomy for complicated appendicitis persists. [6] [27] A recent meta-analysis concluded that laparoscopic appendectomy requires significant resources and surgical expertise to reach maximum efficiency. Therefore, if these technical and surgical criteria cannot be met, open appendectomy should be the surgical treatment of choice. [28]

The best procedure for complicated appendicitis has not been conclusively determined. However, because of continued improvements in the quality and accessibility of computed tomography, the efficacy and feasibility of performing nonoperative management, including targeted intra-abdominal drainage, have increased, and recent evidence supports performing nonoperative management in complicated appendicitis. It is important to note that several studies reported higher rates of recurrence after nonsurgical treatment of complicated appendicitis of up to 38% within 1 year. [29] [30] To avoid this high chance of recurrence, reports suggest routine elective interval appendectomy following nonoperative management; however, because of the consistent morbidity, routine interval appendectomy after successful nonoperative management is not justified in every patient. Overall, despite evidence and the consensus of the World Society of Emergency Surgery, which supports the use of nonoperative management, clinicians continue to seek the most appropriate treatment strategies for complicated appendicitis. [2] The results of our study, performed busing a modeling method, provide valuable information to help surgeons decide the ideal strategy to treat complicated appendicitis, with complex tradeoffs between financial resources and patient utility.

Each country has its own health insurance system. In Japan, the government uses a universal health insurance system; therefore, once included in the health insurance system's listing by the governmental council, expensive imaging studies and emergent surgery can be performed easily in Japan [31]. This has caused a drastic increase in treatment costs, without necessarily indicating feasibility within the public health system. We must maximize the benefits obtained from the available resources, within the system; however, in Japan, evidence is limited regarding the cost-effectiveness of clinical therapeutic strategies. [32] [33] [34] Our findings suggest that Japan's government may need to adjust the clinical recommendations based on cost-effectiveness in acute appendicitis therapy.

Sensitivity analyses in our study indicated that variation in the probability and HRQoL factors for ELA with perioperative complications for complicated appendicitis had a significant influence on outcomes for both nonoperative management with ILA and nonoperative management without ILA. Therefore, we suggest that ELA and its perioperative complications is an important factor in choosing a therapeutic strategy for complicated appendicitis. Randomized control trials have reported postoperative complications following laparoscopic appendectomy for complicated appendicitis. [35] [36] Surprisingly, there were no differences in the incidence of complications compared with open appendectomy, including surgical site infections and intra-abdominal abscess, which are the most common complications following appendectomy. Regarding cost-effectiveness, intra-abdominal abscess is an especially serious

complication and a reported primary drawback of laparoscopic appendectomy. [37] Some authors reported that insufflation and irrigation during laparoscopic appendectomy for complicated appendicitis may increase the incidence of intra-abdominal abscess. [38] [39] This complication leads to a prolonged hospital stay, possible readmission, and the need for subsequent treatment, which increases costs and decreases utility of laparoscopic appendectomy in patients with complicated appendicitis. Therefore, we speculate that in patients with higher risk of postoperative intra-abdominal abscess, such as older patients, nonoperative management could be a preferred and cost-effective strategy compared with operative management.[40]

It should be noted that no consensus exists regarding the threshold for acceptable cost per QALY ratios in Japan's national health policy. Previously, Shiroiwa *et al* reported that <¥5–6 million per QALY is considered cost effective in Japan. [41] However, the study did not consider patient quality of life, and it is impossible to accurately determine cost-effectiveness. Therefore, we adopted the World Health Organization's WTP recommendation for ICER threshold, in our model. This metric is meant to be used solely as a common cognitive anchor rather than as a method of dictating clinical decision-making. Nevertheless, we consider our conclusions in this study robust based on the results of the sensitivity analyses. An acceptability curve showed that the probability of nonoperative management with ILA being the most cost-effective strategy was approximately 50% when WTP was ¥20,000,000. Additionally, the possibility of nonoperative management without ILA being the most cost-effective strategy was always < 25% regardless of WTP, demonstrating that both nonoperative management strategies were not cost-effective over a pragmatic range of values for Japanese health care payers. Therefore, operative management remains a standard strategy, and a price reduction would be necessary for nonoperative management strategies to be considered cost-effective.

This study has several limitations. First, because we focused on cost-effectiveness for a relatively short duration, we did not consider the risk of appendiceal cancer. Some authors recommend routine interval appendectomy to rule out the possibility of malignancy rather than to avoid the risk of recurrence. [7] [42] [43] Recent retrospective studies report that the rate of appendiceal neoplasms in patients undergoing interval appendectomy is especially high in patients with complicated appendicitis ≥ 40 years of age.[42] [43] The rate is substantial, and surgeons should be aware of the risk of malignancy in patients with complicated appendicitis. However, a systematic review and meta-analysis showed a 7.4% incidence of recurrent appendicitis and a 1.2% incidence of malignant neoplasm in patients undergoing successful nonoperative management for complicated appendicitis. Based on these findings, the authors concluded that interval appendectomy is not necessary. [4] The role of appendectomy in complicated appendectomy for oncological reasons is debated. Investigating the cost-effectiveness of appendectomy in complicated appendectomy with a long-term follow-up regarding the possibility of malignancy in the appendix is an area requiring future research.

Second, because of the lack of Japanese studies on this subject, in the present study, the costs of the strategies were estimated using a micro-costing method to obtain precise information of the actual costs paid by the national insurance in a municipal hospital. However, these estimates may be subject to

variations in treatment options between hospitals, even though the variations were included in the sensitivity analysis.

Third, few studies have evaluated quality of life in the early postoperative period after appendectomy. Therefore, we estimated utilities for the treatment strategies based on data related to other diseases and surgical procedures. If the utility of the procedures in patients with complicated appendicitis differed from our assumptions, our model outcomes could be compromised. Further studies are needed to better characterize the health states associated with the treatment of complicated appendicitis.

Finally, our study did not provide sufficient data to assess minor and major complications individually. The impact on cost and utility is strongly influenced by the type of complication; therefore, it should be emphasized that substantial differences in cost and utility of complications could affect the model outcome.

In conclusion, we found that nonoperative management with ILA and nonoperative management without ILA were not cost-effective strategies compared with operative management in the treatment of complicated appendicitis. Nonoperative management deserves serious consideration as a treatment option, but should not be performed routinely in treating complicated appendicitis because of its lower cost-effectiveness.

Declarations

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Disclosures

Kiyoaki Sugiura, Keiichi Suzuki, Tomoshige Umeyama, Kenshi Omagari, Takeo Hashimoto and Akihiko Tamura have no conflicts of interest or financial ties to declare.

Abbreviations

ELA, emergency laparoscopic appendectomy; ILA, interval laparoscopic appendectomy; QALY, quality-adjusted life years; HRQoL, health-related quality life; ICER, incremental cost-effectiveness ratio; WTP, willingness-to-pay

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Tables

Due to technological limitations, tables are only available as downloads in the supplementary files section.

Figures

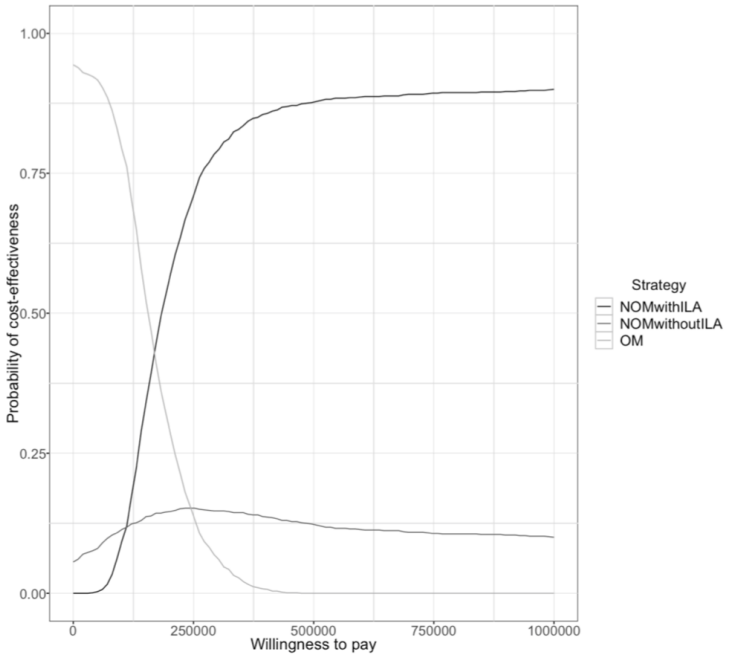

Figure 4. Cost-effectiveness acceptability curve for probabilistic sensitivity analyses.

Figure 1

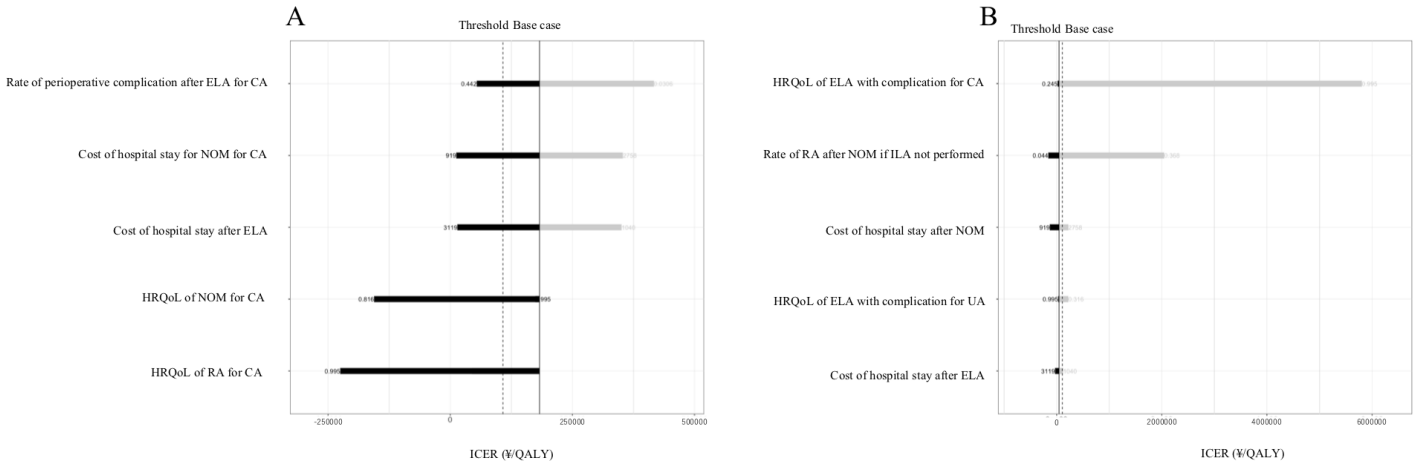

Figure 2. Tornado diagram for one-way sensitivity analysis. A : NOM with ILA, B : NOM without ILA

Figure 2

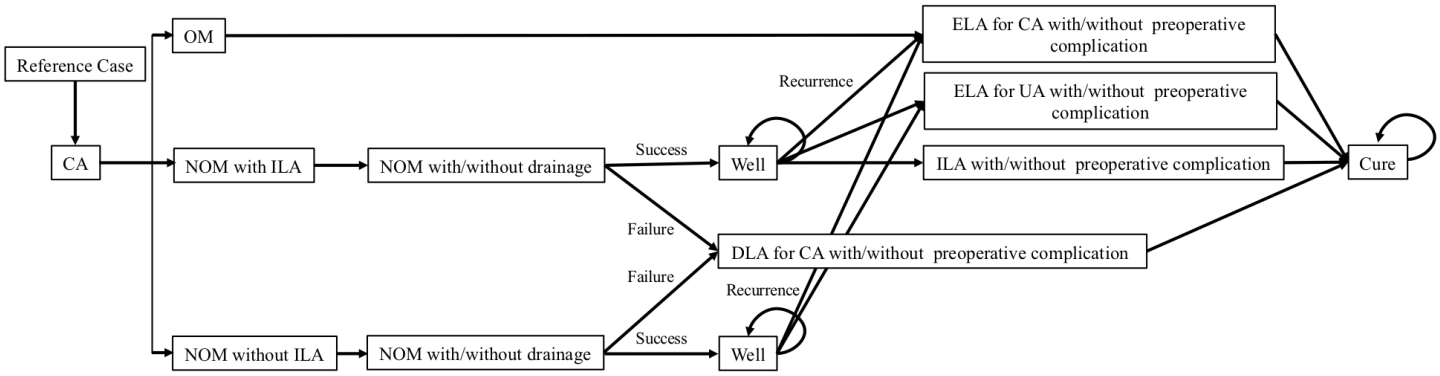

Fig 1. Treatment strategies of CA.

Figure 3

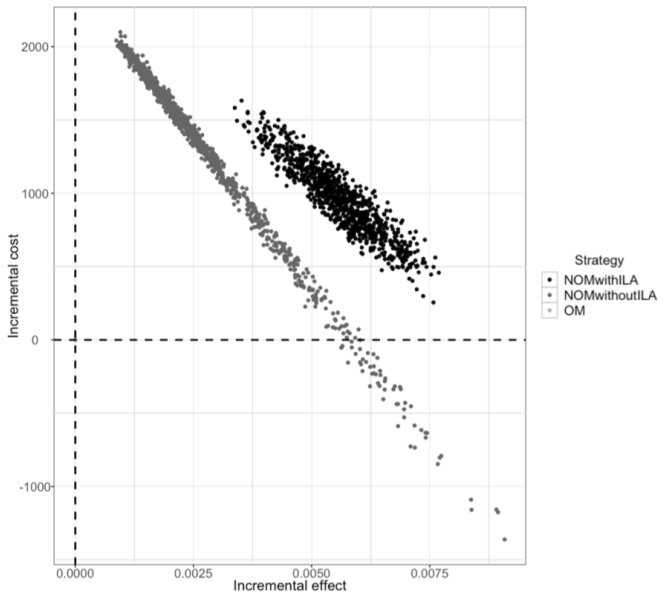

Figure 3. Monte Carlo probabilistic sensitivity analysis

Figure 4

Supplementary Files

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