Original Research Article

MDM Medical Decision Making

Medical Decision Making
2023, Vol. 43(1) 110–124

DOI: 10.1177/0272989X221132256
journals.sagepub.com/home/mdm
SAGE

Utilizing Clinical Trial Data to Assess Timing of Surgical Treatment for Emphysema Patients

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Background. Lung volume reduction surgery (LVRS) and medical therapy are 2 available treatment options in dealing with severe emphysema, which is a chronic lung disease. However, or there are currently limited guidelines on the timing of LVRS for patients with different characteristics. **Objective.** The objective of this study is to assess the timing of receiving LVRS in terms of patient outcomes, taking into consideration a patient's characteristics. **Methods.** A finite-horizon Markov decision process model for patients with severe emphysema was developed to determine the short-term (5 y) and long-term timing of emphysema treatment. Maximizing the expected life expectancy, expected quality-adjusted life-years, and total expected cost of each treatment option were applied as the objective functions of the model. To estimate parameters in the model, the data provided by the National Emphysema Treatment Trial were used. **Results.** The results indicate that the treatment timing strategy for patients with upper-lobe predominant emphysema is to receive LVRS regardless of their specific characteristics. However, for patients with non–upper-lobe–predominant emphysema, the optimal strategy depends on the age, maximum workload level, and forced expiratory volume in 1 second level. **Conclusion.** This study demonstrates the utilization of clinical trial data to gain insights into the timing of surgical treatment for patients with emphysema, considering patient age, observable health condition, and location of emphysema.

Highlights

- Both short-term and long-term Markov decision process models were developed to assess the timing of receiving lung volume reduction surgery in patients with severe emphysema.
- How clinical trial data can be used to estimate the parameters and obtain short-term results from the Markov decision process model is demonstrated.
- The results provide insights into the timing of receiving lung volume reduction surgery as a function of a patient's characteristics, including age, emphysema location, maximum workload, and forced expiratory volume in 1 second level.

Keywords
emphysema, lung volume reduction surgery, Markov decision process, NETT

Date received: September 21, 2021; accepted: September 12, 2022

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According to the United States National Heart, Lung, and Blood Institute (NHLBI), emphysema is one of the main conditions of chronic obstructive pulmonary disease, a progressive lung disease with the primary cause of cigarette smoking. In emphysema, the lung tissue is gradually damaged, especially the walls between the air sacs, which causes difficulties in breathing or prevents the breathing process and eventually leads to death in severe cases. Approximately 3.8 million people are diagnosed with emphysema in the United States, and 90% of patients are older than 45 years.[1]

There does not exist any available cure for emphysema, but some treatments are available to prevent its progression and reduce the severity of symptoms. The standard treatments include lifestyle changes, medicine, pulmonary rehabilitation, oxygen therapy, surgery, and lung transplants.[2] One of the treatments that have been widely studied to determine its effectiveness is lung volume reduction surgery (LVRS). Under LVRS, the damaged tissues that cause disorders in lung function are resected so that the remaining parts of the lungs have enough space to expand properly.[3]

To reliably study the advantages and disadvantages of LVRS, the NHLBI and 2 other health centers have conducted a clinical trial called the National Emphysema Treatment Trial (NETT). The main goals of the NETT were to identify the benefits and risks of LVRS, how long the benefits last, and patients who have better responses to the surgery in comparison with other treatments.[4] Patients with severe emphysema went through 6 to 10 rehabilitation programs with medicine and oxygen therapy in 17 clinics. Then, 1,218 patients eligible for the experiment were randomly assigned to undergo LVRS or continue the medical treatment. The medical treatment in NETT follows the general guidelines for treating emphysema, including smoking cessation, bronchodilators, oxygen therapy, immunization, and pulmonary rehabilitation.[2] The NETT collected the patients' data from different perspectives, such as exercise capacity, quality of life, cardiovascular function, and radiologic tests, for 5 consecutive years. The NETT is a valuable data set for studying emphysema and its treatments.

Many research studies have been devoted to recognizing new facts about LVRS and emphysema. Most of the studies focused on demonstrating the advantages and disadvantages of the surgery over medical treatment. Considering the results of all patients, those who received LVRS were more likely to have an improvement in exercise capacity, forced expiratory volume in 1 second (FEV_1) percent predicted, level of dyspnea, and quality of life.[5,6] However, there are short-term mortality risks associated with the patients who received LVRS.[7] The 90-d mortality rate in the LVRS group was 7.9%, while the medical treatment group had a 1.3% mortality rate.[8] The 1-y postoperative risk mortality for the LVRS group is significantly higher, and the 3-y risk mortality is equal to the medical treatment group, but after 4 y, it has a significantly lower risk.[5]

Emphysema patients can be divided into non–high-risk and high-risk subgroups. According to NETT, high-risk patients are those who have FEV_1 values less than 20% of the predicted and either a very low carbon monoxide diffusing capacity or homogeneous emphysema. This group of patients has a higher mortality rate when undergoing LVRS compared with medical treatment, and the survivors do not have meaningful improvements in their lung function, exercise capacity, or quality of life.[9,10]

Among the non–high-risk patients, specific subgroups benefited more from LVRS. The emphysema pattern on chest computed tomography (upper-lobe and non–upper-lobe predominant emphysema) and the level of maximal exercise capacity at the beginning of the trial are 2 significant factors in predicting the advantages of LVRS over medical treatment. Patients with the upper-lobe–predominant emphysema and lower exercise capacity have better survival and improvement in their exercise capacity and quality of life after undergoing LVRS compared with medical treatment.[5,11]

In addition to the benefits and risks of LVRS, it is a costly procedure. Previous cost-effectiveness analyses have indicated that the only subgroup for whom LVRS is a cost-effective treatment option is the group with upper-lobe–predominant emphysema and low exercise capacity. For other subgroups of patients, the cost of LVRS is not justifiable when considering quality-adjusted life-years (QALYs).[12]

This study aims to assess the optimal timing of performing LVRS considering patients' characteristics, including age, location of emphysema, maximum workload, and FEV_1 level. In chronic disease management,

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data-driven decision making over time can improve patients' life expectancy and quality of life. The Markov decision process (MDP) is a powerful tool that can provide a personalized treatment strategy based on the available information.[13] MDPs have been widely used in chronic disease treatment analysis where sequential decision making is needed.[14,15] Some of the applications of MDPs in chronic diseases are optimizing the time of the initial HIV treatment,[16] breast cancer treatments,[17] liver transplant,[18] and type 2 diabetes treatments.[19,20]

Randomized clinical trials (RCTs) are designed to study the efficacy and safety of a new treatment compared with the standard treatment or a placebo group. RCT data are widely used to determine the benefits and disadvantages of a new treatment, often for a particular patient group. A wide variety of variables are measured regularly in RCTs to enable researchers to thoroughly study the new treatment and its effect on the patients. However, using RCTs directly to determine the best timing of treatment initiation based on patients' characteristics is challenging, considering the size of the study population, duration of follow-up, and so forth. In this study, we demonstrate the use of RCTs with limited follow-up data to evaluate patient outcomes under various treatment timing considering individualized characteristics.

Methods

To determine the optimal time of performing LVRS on each patient, a finite-horizon discrete-time Markov decision process model is proposed. We assume that each patient will be examined by a specialist every year. If the chosen action is to receive LVRS, the patient will undergo surgery immediately, but if the decision is to wait for another year, the patient will have medical treatment until the next annual visit.

Model Formulation

The main components of each MDP model are decision epochs, state space, action space, transition probabilities, and rewards.[21] In the following sections, we define each component of the MDP model for the emphysema treatment problem. Figure 1 also depicts the states, transitions, and actions in the MDP model.

Decision epoch. We assessed the timing of performing LVRS, considering both short-term and long-term results. Because patients had annual visits with specialists and had their data collected during the NETT study, the evaluations were conducted annually in both short-term and long-term models. We define T as the annual decision epoch set from 0 to N, where $N < \infty$ is the last decision epoch. For the short-term model, the decision epochs are years after starting the trial, and the last decision epoch is 5, since the NETT study has 5 y of follow-up data. For the long-term model, the decision epochs are years after age 50, because most patients with severe emphysema are older than 50 y in the NETT data set. The patients will be followed until the age of 80 y, for whom we have a full set of data.

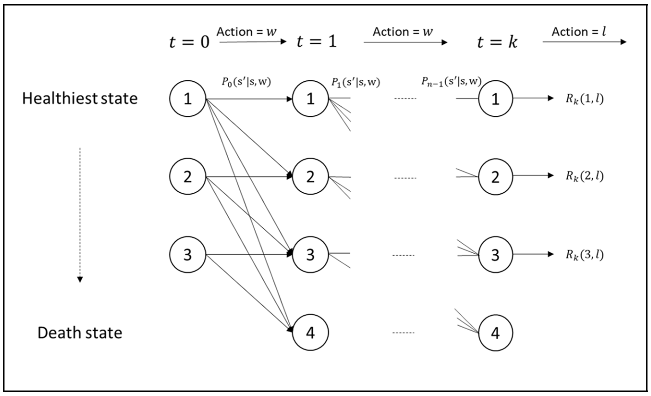

Figure 1 Emphysema Markov decision process states and transitions when lung volume reduction surgery (LVRS) is performed at decision epoch k (w = wait, l = LVRS).

State space. To make an accurate decision at each decision epoch, the states of the system should sufficiently represent the patients' health status. We consider 2 types of observable states as the health states of our model: the amount of FEV_1, which is the maximal amount of air one can forcefully exhale in 1 s. FEV_1 is often converted to the percentage of normal value and can have a range of 0% to 100% of predicted. This measurement is one of the common ways of assessing airway obstruction in emphysema. The other measurement is maximal workload, which is generally used to differentiate the patients who will benefit from LVRS or not. Patients with lower maximal workload have a lower risk of mortality and a higher chance of improvement in maximal workload and quality of life score after 24 months.[8]

We separately define 4 states in our state space S for FEV_1 and maximal workload due to sample size. In NETT, patients with severe emphysema are randomized to one of the treatments, and the range of FEV_1 among the patients at the beginning of the trial is between 8% and 54% predicted. We divide this range into 3 subgroups as our states, that is, High (State 1), Medium

Table 1 State Definition Based on FEV_1 and Maximum Workload (Maxwk)

	State		
Sex	**High (State 1)**	**Medium (State 2)**	**Low (State 3)**
Female and male	$FEV_1 \geq 35$	$25 \leq FEV_1 < 35$	$FEV_1 > 25$
Female	Maxwk ≥ 33	$25 \leq$ Maxwk < 33	Maxwk > 25
Male	Maxwk ≥ 53	$38 \leq$ Maxwk < 53	Maxwk > 38

(State 2), and Low (State 3), in which the high state is the healthiest and the low state is the most severe. The last state in the model is the Death state (State 4), which is an absorbing state. The process of defining the states is the same when the maximal workload is used. However, because the maximal workload is a measurement of physical performance, the states are defined on a different scale for male and female patients.The maximal workload and FEV_1 levels are decided such that the 5-y QALYs are statistically different among the states and the number of patients in each state is acceptable to reliably estimate transition probabilities. The cutoff points for both models are presented in Table 1.

Action space. At each decision epoch, 2 actions are possible in the action space A, performing LVRS on the patient at that year (l) or waiting for another year (w) and deciding again at the next decision epoch, that is, $A = \{w, l\}$. The waiting action is to continue medical treatment alone (MTA) for another year.

Transition probabilities. Transition probability indicates the probability of transferring from state s to state s' in the next decision epoch when the chosen action is to continue medical treatment (w). The probability of remaining in State 4 (Death) is $P(4|4, w) = 1$, and the probability of transitioning from State 4 to other states is $P(s|4, w) = 0, s \in \{1, 2, 3\}$. In general, $P(s'|s, w)$ is the probability of transitioning from state s to s' when the chosen action is to wait (MTA).

Rewards. We consider the expected remaining life-years, expected QALYs, and total expected cost (only in the short-term) as separate objectives of our models.

- $R_t(s, l)$ is the lump sum reward that a patient in state s, where $s \in \{1, 2, 3\}$, receives for the rest of their life when the chosen action is to receive LVRS at decision epoch t.
- $r_t(s, w)$ is the immediate reward that a patient in state s, where $s \in \{1, 2, 3\}$, receives for 1 y when the chosen action is to continue medication at decision epoch t. The immediate reward of the death state is zero ($r_t(4) = 0$).
- $R_N(s, l)$ is the terminal reward that a patient in state s, where $s \in \{1, 2, 3\}$, receives for the rest of their life when the chosen action is to receive LVRS at the last decision epoch N.
- $R_N(s, w)$ is the terminal reward that a patient in state s, where $s \in \{1, 2, 3\}$, receives for the rest of their life when the chosen action is to continue medication at the last decision epoch N.

Optimal policy. The goal of our MDP models for emphysema is to find the optimal policy that represents the best timing of LVRS treatment, considering the patient's characteristics. The optimal solution of the model can be obtained by using the backward induction method and solving the following equations for all $t \in \{0, 1, \ldots, N-1\}$ and $s \in \{1, 2, 3\}$.

$$V_t(s) = \max\{R_t(s, l), r_t(s, w) + \lambda \sum_{s' \in s} P_t(s'|s, w) V_{t+1}(s')\},$$

where $V_t(s)$ is the total expected reward of state s at decision epoch, t, and λ is the annual discount factor. The total expected reward of the last decision epoch N is calculated using the following equation.

$$V_N(s) = \max\{R_N(s, l), R_N(s, w)\}.$$

Parameter Estimation

Data. We use the National Emphysema Treatment Trial (NETT) data for this study, which is a randomized multicenter trial to study the effects of LVRS on patients with severe emphysema. The data were collected before randomization and at 6, 12, 24, 36, 48, and 60 mo after randomization. The NETT data set has been updated to include additional follow-up for vital status and death

Table 2. Summary of the NETT Study Population[a]

Characteristic	LVRS (n = 608)	MTA (n = 610)
Age, y	66.5 ± 6.3	66.7 ± 5.9
Sex, n (%)		
Female	253 (42)	219 (36)
Male	355 (58)	391 (64)
Race, n (%)		
Non-Hispanic White	581 (96)	575 (94)
Non-Hispanic Black	19 (3)	23 (4)
Other	8 (1)	12 (2)
Emphysema, n (%)[b]		
Upper lobe	345 (57)	364 (60)
Non–upper lobe	193 (32)	176 (29)
High risk	70 (11)	70 (11)
Maximum workload (W)	38.7 ± 21.1	39.4 ± 22.2
FEV_1% predicted	26.8 ± 7.4	26.7 ± 7.0
Average daily QWB	0.58 ± 0.12	0.56 ± 0.11
90-d mortality (%)	7.9 (5.9–10.3)	1.3 (0.6–2.6)

LVRS, lung volume reduction surgery; MTA, medical treatment alone; NETT, National Emphysema Treatment Trial.
[a]All of the values are based on the baseline report.
[b]Patients with severe emphysema are divided into 3 subgroups: high-risk patients, non–high-risk patients with upper-lobe–predominant emphysema, and non–upper-lobe–predominant emphysema.

dates of the patients through June 3, 2013. In NETT, participating patients completed a pulmonary rehabilitation program including education, counseling, and exercise training. They also received medicines and oxygen as needed. Then, they were randomly assigned to either continue this treatment (MTA) or undergo LVRS in addition to the medication. We use the MTA results to estimate transition probabilities for the delayed treatment group.

The NETT patients' baseline information is summarized in Table 2. Patients with severe emphysema are divided into 3 subgroups: high-risk patients, non–high-risk patients with upper-lobe–predominant emphysema, and non–upper-lobe–predominant emphysema.

Estimation of the transition probabilities. Two separate state representations are considered for modeling patient health states: maximum workload and FEV_1. For each set of health states, the data at the time of randomization and 5 y of follow-up are collected in the NETT data set. Using these 5 y of consecutive data for a patient, we can follow the transition between states from each decision epoch to the next. We applied the maximum likelihood estimation method to estimate the transition matrix[22] of each subgroup of patients stratified based on age and location of emphysema. The transition probabilities for each subgroup c_k is estimated using the following equation, where n_{ijk} is the number of times that patients of group c_k changed from state i to state j after 1 y and n_{ik} is the number of times patients of group c_k have been in state i in all years.

$$\hat{P}_{ij}^{MLE}(c_k) = P_{c_k}(s_{t+1} = j | s_t = i) = n_{ijk} / \sum_{j=1}^{4} n_{ijk}$$

To characterize the statistical uncertainty for the transition probabilities, the Efron's bootstrap is used to construct the confidence intervals of the transition probabilities for each specific subgroup of patients (i.e., upper-lobe, non–upper-lobe, and high-risk patients).[22] Bootstrap samples generate a new set of transition counts for row i assuming a multinomial distribution with probabilities of $\hat{P}_{ij}^{MLE}$. Repeating the sampling process multiple times, we can find the confidence intervals for the transition probabilities.

Estimation of the rewards. Different criteria are considered as the rewards in this study: life expectancy, QALYs, and cost. The new update of the NETT data set contains the mortality information based on the number of days after randomization and the vital status (dead or alive) until June 3, 2013. A Cox proportional hazards regression model[23] for each treatment group (LVRS and medical treatment) is used to measure the effects (hazard rates) of age, state, and the location of emphysema on the remaining lifetime of the patients and estimate the

Table 3 Mean Direct Medical Cost According to the Time after the Start of the Trial[31]

Mean Direct Cost, $		
	Medical Treatment	**Lung Volume Reduction Surgery**
First year	25,151	97,718
Second year	25,008	15,141
Third year	19,662	16,299

expected life years based on these covariates. The survival analysis is performed using the flexsurv R package.[24] The results of the Cox proportional hazards model and justification of the use of this survival analysis method for this problem are provided in the online appendix.

To calculate QALYs, the Quality of Well-Being Scale (QWB), which has a range between 0 (death) and 1 (optimum health), is used as the quality-of-life measurement.[25] QWB is a comprehensive scale that asks about 58-item symptoms and problems and covers acute and chronic symptoms, self-care, mobility, physical activity and functioning, and social activity.[26] The QWB scale has been used in other medical conditions such as diabetes,[27] depression,[28] HIV,[29] and cystic fibrosis.[30]

Short- and Long-term Models

We developed both short-term and long-term MDP models. In the short-term model, a 5-y time horizon is considered to compare different policies first based on the expected life-years, expected QALYs, and total expected cost in 5 y. We did not consider cost as our objective in the long-term model because of the lack of data on costs associated with LVRS in long term. We optimized the expected QALYs in the remaining life-years of the patients in the long-term model. The decision of when to initiate LVRS is made based on each patient's health state, age, and location of emphysema.

We used the direct mean cost reported by the NETT group,[31] which includes Medicare reimbursement and pharmacy cost, to compare the policies. The direct mean cost of each treatment option for the first 3 y after the beginning of the trial is presented in Table 3. We assumed that after the third year, the annual treatment cost remains the same. There is no significant change in the treatments that both groups receive in and after the fourth year, in comparison with the third year. In the LVRS group, the first year's cost is notably higher because of the high cost of surgery and hospitalization. Because of the rehabilitation program, the first year's cost is slightly higher in the MTA group compared with later years.

To evaluate the impact of treatment costs on the optimal policy, the net monetary benefit (NMB) is used as the objective function in addition to the life expectancy and QALYs. NMB quantifies the value of a policy based on the expected QALYs of that policy and willingness to pay per QALY. NMB is calculated with this equation: $NMB = \alpha \times QALY - Cost$, where α is the willingness to pay per QALY.

Short-term model. Lung function and exercise testing are part of the guidelines for treating patients with severe emphysema.[32] Therefore, the initial state of the patients with severe emphysema is fully observable. For each subgroup of patients based on initial state, age category, and location of emphysema, 6 different policies are available in a 5-y time horizon.

- Policy 1: performing LVRS at the beginning of the trial
- Policy 2: receiving standard medical treatment for 1 y and performing LVRS at the beginning of the second year
- Policy 3: receiving standard medical treatment for 2 y and performing LVRS at the beginning of the third year
- Policy 4: receiving standard medical treatment for 3 y and performing LVRS at the beginning of the fourth year
- Policy 5: receiving standard medical treatment for 4 y and performing LVRS at the beginning of the fifth year
- Policy 6: receiving standard medical treatment for 5 consecutive years

The policies are evaluated based on the total expected rewards calculated using the following equation:

$$R_i(s) = P(s'|s, w) \sum_{t=1}^{i-1} r_t(s, w) + R_i(s, l) \quad , \forall i = 1, \ldots, 6,$$

where $R_i(s)$ is the total reward of policy i (i.e., LVRS is performed at the beginning of i^{th} year) and $R_i(s, l)$ is the lump sum reward of performing LVRS at the beginning of i^{th} year.

Long-term model. The backward induction method is applied to solve the long-term MDP models and determine the optimal solution for both the expected remaining life-years and the expected QALYs as the rewards. The optimal policy is the best action of "continue medical treatment" or "perform LVRS" at each age that maximizes the total rewards. The model is developed for patients between ages 51 y (the first decision epoch) and 80 y (the last decision epoch), as more than 97% of NETT patients are between these ages. Two separate models are also built considering 3 levels of maximum workload and 3 levels of FEV_1 percent predicted as the health states.

The current state definition of the MDP model is based on the maximum workload or FEV_1 separately, due to the limited number of patients, only 5 y of follow-up data, and high missing values. Jointly considering 3 levels of maximum workload and 3 levels of FEV_1 as the states results in 10 states, which makes the parameter estimation more difficult. However, we are interested in combining the states and comparing the results with the separate models. To deal with the data limitation, we considered only 2 levels, high and low, for the maximum workload and FEV_1. The details of this model and the results are explained in the online Appendix.

Stratification. In the NETT data set, patients are divided into 3 groups, upper-lobe–predominant emphysema, non–upper-lobe–predominant emphysema, and high-risk patients. Similar to this division, separate models are developed for upper-lobe, non–upper-lobe, and high-risk patients. We also stratified the patients for the short-term models into 2 groups based on their age: patients aged ≤ 67 y and patients aged >67 y. Age is one of the important factors in predicting mortality after LVRS.[4] The age of 67 y is derived based on a decision tree analysis. The response variable is the 5-y QALY, and the input variables are age and location of emphysema. For each feature k, the decision tree algorithm finds the best split value b that minimizes the variation of the response in each node.[33] The 2 nodes are $R_1(k,b) = \{x|x(k) \leq b\}$ and $R_2(k,b) = \{x|x(k) > b\}$. The best split y for feature k is calculated based on the following equation:

$$\min_b\left[\min_{c_1} \sum_{x_i \in R_1(k,b)} (y_i - c_1)^2 + \min_{c_2} \sum_{x_i \in R_2(k,b)} (y_i - c_2)^2\right],$$

where

$$c_1 = mean(y_i | x_i \in R_1(k,b)),$$

$$c_2 = mean(y_i | x_i \in R_2(k,b)).$$

Sensitivity Analysis

To estimate the robustness of the long-term model considering different parameters, we changed the discount factor and the transition probabilities in the range of their confidence interval and compared the results with the optimal decision. In the next step, both univariate and multivariate probabilistic sensitivity analyses are based on the proposed method by Chen et al.[34] The purpose of the univariate analysis is to find the sensitivity of the baseline model to one parameter (θ_j) at a time. In this method, the parameter j values are sampled among the estimated range of the bootstrap method, and the MDP is solved to find the optimal policy considering the change in parameter j. Two policies are considered as similar if the objective values are only $\delta \times 100\%$ different from each other (e.g., $\delta = 0.01$). The confidence in the baseline policy is defined as the percentage of times that the sampled objective value is similar to the base case objective value.

$$\alpha(j) = P\{V(\theta^i, \pi^0) \geq (1-\delta)V(\theta^i, \pi^i)\},$$

where $\theta^i = (\theta_1^0, \ldots, \theta_j^i, \ldots, \theta_p^0)$.

In the multivariate analysis, multiple parameters are sampled randomly, and the optimal sampled policy π^i is found. The relative difference between the sampled policy optimal objective value ($V(\theta^i, \pi^i)$) and the baseline policy objective value with respect to the sampled parameters ($V(\theta^i, \pi^0)$) shows the acceptance of the base policy. The relative gap is calculated using the following equation.

$$\delta_r = \frac{V(\theta^i, \pi^i) - V(\theta^i, \pi^0)}{V(\theta^i, \pi^i)}$$

If the relative gap is less than $\delta \times 100\%$, the baseline policy is acceptable. Ranging the tolerance from 0% to 100%, we can calculate the probability of accepting the baseline policy as the number of times the sampled data are acceptable over all samples.

All of the analyses were performed using the statistical computing language R version 3.6.[35]

Results

Short-term Results

Table 4 compares the policies based on the short-term expected life-years in each subgroup of patients. In patients aged ≤ 67 y with upper-lobe emphysema, those with a higher maximum workload should wait 4 or 5 y to receive the most short-term expected life-years, whereas

Table 4 Short-term Expected Life-Years for Different Policies Based on Patient Characteristics and Maximum Workload[a]

Subgroup Characteristic	Health State	Policy 1	Policy 2	Policy 3	Policy 4	Policy 5	Policy 6
Patients aged ≤ 67 y with upper-lobe emphysema	High	4.16	4.07	4.24	4.31	4.34[b]	4.34[b]
	Medium	4.50[b]	3.89	4.00	4.06	4.08	4.08
	Low	4.47[b]	3.18	3.26	3.31	3.33	3.33
Patients aged ≤ 67 y with non–upper-lobe emphysema	High	3.88	3.89	4.21	4.41	4.56	4.64[b]
	Medium	3.33	3.08	3.33	3.49	3.61	3.69[b]
	Low	4.21[b]	3.37	3.51	3.62	3.70	3.77
Patients aged >67 y with upper-lobe emphysema	High	4.13[b]	3.68	3.81	3.89	3.94	3.94
	Medium	3.96[b]	3.34	3.48	3.56	3.63	3.64
	Low	4.21[b]	3.02	3.13	3.20	3.26	3.29
Patients aged >67 y with non–upper-lobe emphysema	High	3.48	3.48	3.74	3.90	3.99[b]	4.00[b]
	Medium	3.67	3.39	3.59	3.73	3.82	3.88[b]
	Low	4.11[b]	2.71	2.83	2.90	2.97	3.00

[a]Policy i is performing lung volume reduction surgery at the beginning of the i^{th} year for $i = 1, 2, 3, 4$, and 5, and policy 6 is to continue medication for 5 consecutive years.
[b]The policy with the highest total expected rewards.

those with medium or low maximum workload have higher total expected rewards when undergoing LVRS at the earlier time. However, in patients aged >67 y with upper-lobe emphysema, all patients obtain the most short-term expected life-years when having LVRS in the first year. The 2 age groups of patients who have non–upper-lobe emphysema have the same results; that is, those with high and medium maximum workload should continue medication, and those with low maximum workload should undergo LVRS at the beginning to have the most total expected rewards.

The total expected QALYs for the LVRS group and the 1-y expected QALY for the MTA group were calculated. We assumed that the 1-y expected QALY of the MTA group does not depend on the number of years patients have been under medical treatment. This was justified by performing a repeated-measures analysis of variance (ANOVA) test comparing the expected QALY values in different years after the medical treatment, and they were found to be statistically nonsignificant as long as the beginning state and the age group were the same. Results of the repeated-measures ANOVA are provided in the online appendix.

The location of emphysema is an essential factor in dividing the patients based on the benefits of undergoing LVRS.[5] The 2 age groups of patients are subcategorized into upper-lobe– and non–upper-lobe–predominant emphysema. We first consider only the maximum QALYs to determine the best policy. Considering only QALYs of a policy, the policy with the highest QALYs is recognized as the best option for each specific group of patients. Figure 2 shows the expected QALYs of each policy for subgroups of patients by age and location of emphysema. In patients aged ≤ 67 y with upper-lobe–predominant emphysema, patients with low maximum workload have significantly higher mean QALYs when undergoing LVRS at the beginning of the trial (Policy 1) in comparison to Policy 6. The 2 other maximum workload level groups gain higher mean QALYs waiting for 3 y and then undergoing LVRS. On the other hand, patients aged ≤ 67 y with non–upper-lobe emphysema obtain higher rewards remaining in medical treatment. In patients aged >67 y, the location of emphysema does not affect the results of the model, and Policy 1 is the best for low and medium maximum workload groups of patients, whereas receiving surgery after 2 y is a better option.

Figure 3 presents the results of the NMB cost-effectiveness analysis. As shown in this figure, Policy 6 is the best policy, with willingness-to-pay thresholds of \$50,000 to \$100,000 in almost every subgroup of patients. The only exception is patients aged ≤ 67 y with upper-lobe emphysema and low maximum workload. For willingness-to-pay thresholds greater than \$70,000, Policy 1 has the highest NMB.

Long-term Results

In the models with only life expectancy as the reward, receiving LVRS always has higher expected rewards, which shows that patients have higher expected remaining life-years if undergoing surgery immediately after being diagnosed with severe emphysema. Tables 5 and 6 display the results for QALYs as the expected rewards for each age from 51 to 80 y, considering the maximum workload and the FEV_1 percent predicted as states in the MDP models, respectively.

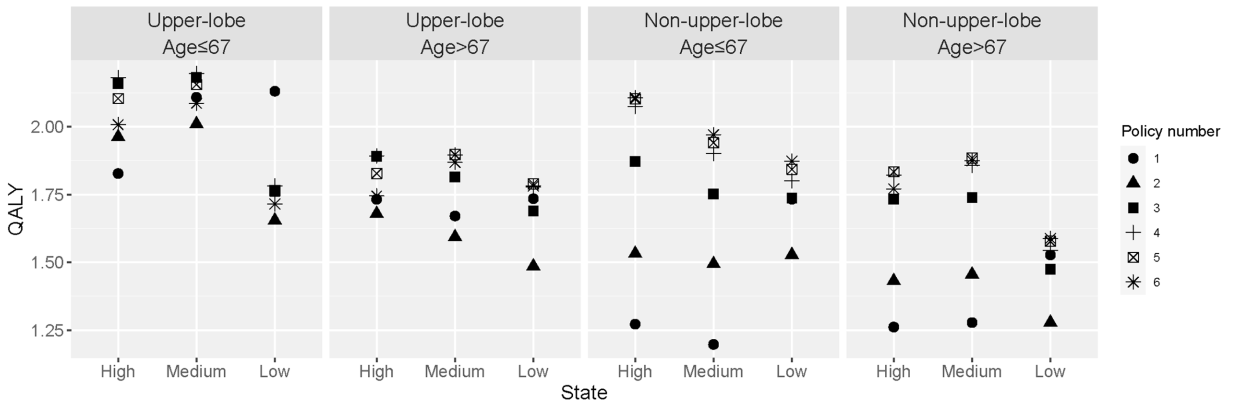

Figure 2 Total expected quality-adjusted life-years (QALYs) of each policy number based on the location of emphysema, age, and starting health state.

Table 5 shows the optimal decision at each age considering the maximum workload level (with high, medium, and low states) and location of emphysema (i.e., upper-lobe, non–upper-lobe, or high-risk patients). The results for patients with upper-lobe–predominant emphysema indicate that this subgroup has higher expected QALYs when receiving surgery as soon as being diagnosed with severe emphysema. Age and maximum workload levels do not influence the optimal policy. In patients with non–upper-lobe emphysema, the optimal solution for patients with a high maximum workload state is to receive surgery for age ≤ 67 y, and for age >67 y, the optimal solution is to continue on medical treatment. The switching age for patients with a medium maximum workload is 72 y. For those with a low maximum workload, undergoing LVRS is the best policy for all ages. The special case is the high-risk patient subgroup, in which the optimal solution is to remain in medical treatment in all ages.

Table 5 indicates the optimal decision at each age considering the FEV_1 level and location of emphysema (upper-lobe or non–upper-lobe patients). In the upper-lobe subgroup of patients, receiving LVRS is always the optimal decision. While in the non–upper-lobe subgroup, patients with high FEV_1 should receive LVRS as soon as being diagnosed with severe emphysema, patients with medium and low FEV_1 have the most expected QALYs when receiving LVRS if they are aged less than 71 and 68 y, respectively. The high-risk subgroup of patients is not considered in this model, because one of the important criteria to identify the high-risk patients is the level of FEV_1, which has been taken into account in defining the states.

We also compared the total expected QALYs of the optimal policy based on the MDP model with a status quo policy. The current guideline by the American Lung Association is that LVRS is most suitable for patients with severe emphysema aged less than 75 to 80 y with upper-lobe emphysema.[36] We compared the expected QALYs of the MDP model with this status quo policy in Figure 4. It can be seen that the total expected rewards are similar before the age of 75 y for upper-lobe patients. However, after age 75 y and for all non–upper-lobe patients, the MDP model has higher total rewards.

Sensitivity Analysis

The results of the MDP model that jointly combines 2 levels of maximum workload and 2 levels of FEV_1 are consistent with the results of the separate models in the treatment recommendation based on the location of emphysema, age, and health states in most cases. The main difference between the 2 models is the age that the optimal decision changes from receiving LVRS to MTA. Therefore, the detailed results of the joint model are reported only in the online appendix.

The results of the sensitivity analyses on different parameters in the model are provided. First, various discount factors are applied in the model, and the results are shown in Table 7. It can be observed that when the discount factor is lower, the optimal age to start LVRS is greater, but the difference is small. To estimate the confidence intervals of the transition probabilities, we used the bootstrap method. The probability of transitioning from any nonabsorbing state to the absorbing (death)

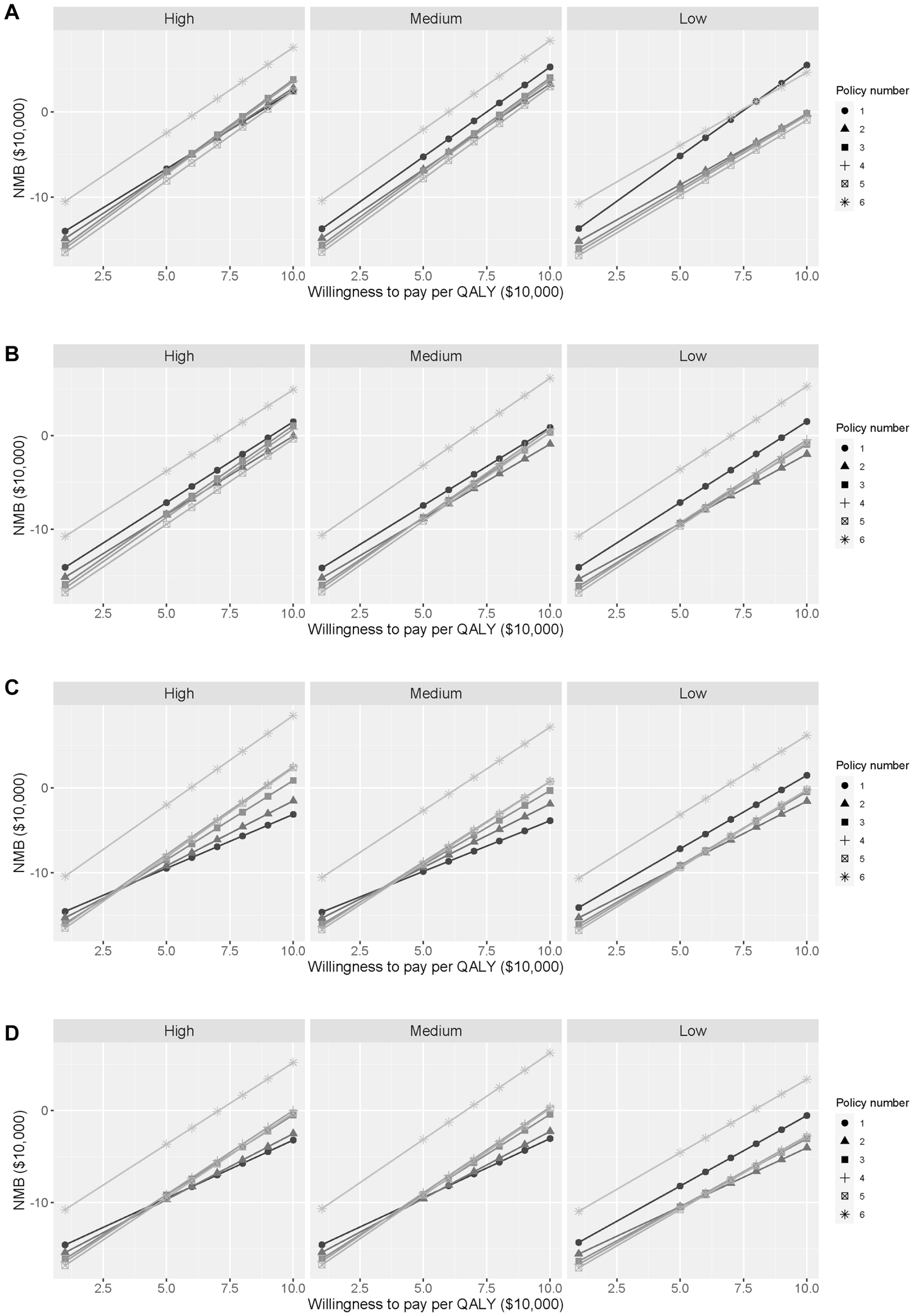

Figure 3 Net monetary benefit (NMB) for different willingness to pay per quality-adjusted life-year (QALY) thresholds of each policy based on the location of emphysema, age, and the starting health state. (a) Patients aged ≤67 y with upper-lobe emphysema. (b) Patients aged >67 y with upper-lobe emphysema. (c) Patients aged ≤67 with non–upper-lobe emphysema. (d) Patients aged >67 y with non–upper-lobe emphysema.

Table 5 Optimal Action Based on the Long-term Quality-Adjusted Life-Years Considering Patients' Age and Maximum Workload Level and Location of Emphysema[a]

Location of Emphysema	State	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80
High Risk	High																														
	Medium																														
	Low																														
Non–upper lobe	High																														
	Medium																														
	Low																														
Upper lobe	High																														
	Medium																														
	Low																														

[a]Darker cells represent the lung volume reduction surgery action, and lighter cells represent the medical treatment alone action.

Table 6 Optimal Action Based on the Long-term Quality-Adjusted Life-Years Considering Patients' Age and FEV_1 Level and Location of Emphysema[a]

Location of Emphysema	State	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80
Upper lobe	High																														
	Medium																														
	Low																														
Non–upper lobe	High																														
	Medium																														
	Low																														

[a]Darker cells represent the lung volume reduction surgery action, and lighter cells represent the medical treatment alone action.

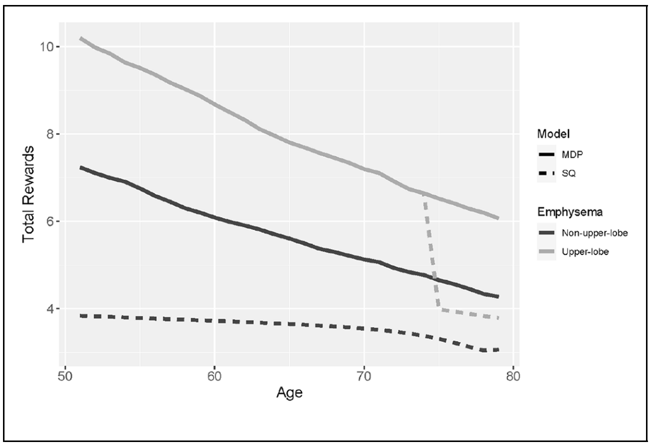

Figure 4 Compating the results of the Markov decision process (MDP) model with the status quo (SQ) policy.

state has a significant effect on the optimal solution of the model. We vary the estimates of the probabilities from −25% to +25%. Note that the other probabilities are updated as well to satisfy the Markov chain requirement while maintaining the relative relationship between these probabilities. It can be seen from Table 8 that the optimal solution of the model highly depends on the probability of transitioning to the death state.

Figure 5 presents the results of the univariate sensitivity analysis for both maximum workload (Figure 5a) and FEV_1 (Figure 5b) as the health states. The confidence in baseline policy is the most sensitive to the estimation of the discount factor and transition probabilities from health states and less sensitive to the QALY estimation. The results are separated based on location of emphysema (upper-lobe and non–upper-lobe) as well. The confidence in the baseline policy for the upper-lobe emphysema is always higher when the parameters are sampled. Figure 6 shows the results for the multivariate sensitivity analysis for maximum workload (Figure 6a) and FEV_1 (Figure 6b) as the health states and location of emphysema. For the same level of relative gap, the probability of accepting the baseline policy is higher when the states are based on the level of maximum workload.

Table 7 Age for Which the Optimal Decision Changes from LVRS to MTA for Patients with Non–upper-lobe–predominant Emphysema under Different Discount Factors[a]

	Maximum Workload Level			FEV_1 Level		
Discount Factor	**Low**	**Medium**	**High**	**Low**	**Medium**	**High**
1	∞	72	63	65	68	∞
0.99	∞	73	65	66	69	∞
0.98	∞	74	66	67	70	∞
0.97	∞	75	67	68	71	∞
0.96	∞	76	68	69	72	∞
0.95	∞	76	69	70	73	∞

LVRS, lung volume reduction surgery; MTA, medical treatment alone.
[a]Switching age of ∞ indicates that LVRS is the best option in all ages.

Table 8 Age for Which the Optimal Decision Changes from LVRS to MTA as the Optimal Action for Patients with Non–upper-lobe–predominant Emphysema under Different Probabilities of Transitioning from Each State to the Death State[a]

	Maximum Workload Level			FEV_1 Level		
Percentage Change[b]	**Low**	**Medium**	**High**	**Low**	**Medium**	**High**
−25	∞	67	60	65	68	∞
−20	∞	67	62	66	69	∞
−15	∞	70	64	67	70	∞
−10	∞	72	65	68	71	∞
−5	∞	74	66	69	72	∞
0	∞	76	66	70	73	∞
+5	∞	79	68	71	74	∞
+10	∞	∞	70	73	76	∞
+15	∞	∞	71	74	77	∞
+20	∞	∞	72	76	79	∞
+25	∞	∞	73	75	∞	∞

LVRS, lung volume reduction surgery; MTA, medical treatment alone.
[a]Switching age of ∞ indicates that LVRS is the best option in all ages.
[b]Percentage of the probability added (+) to or subtracted from (−) the bootstrap estimates.

Discussion

The objective of this study was to determine the optimal treatment strategy considering a patient's characteristics. We achieved this by developing Markov decision process models for various subgroups of patients considering the expected remaining life-years, QALYs, and cost. We observed that patients with upper-lobe–predominant emphysema have a higher life expectancy and QALYs when undergoing LVRS following the diagnosis of severe emphysema. However, the optimal strategy for patients with non–upper-lobe–predominant emphysema depends on the age of the patient, maximum workload level status, and FEV_1 level. The outcomes revealed that receiving LVRS results in higher expected rewards in patients aged ≤ 67 y. The switching age (i.e., the age at which the optimal action changes) was affected by the maximum workload and FEV_1. The higher maximum workload and higher FEV_1 resulted in an earlier switching age.

As explained in the "Methods" section, the current state definition of our MDP model is based on 3-level maximum workload or FEV_1 separately. This is due to the limited number of patients, short follow-up data (only 5 y), and high missing values. We were interested in combining the states and compareing the results with the separate models. However, jointly considering 3 levels of maximum workload and 3 levels of FEV_1 as the states makes the parameter estimation more challenging. Therefore, we considered only 2 levels, high and low, for the maximum workload and FEV_1. The results of the joint model are consistent with the results of the separate models in the treatment recommendation based on the location of emphysema, age, and health states in most

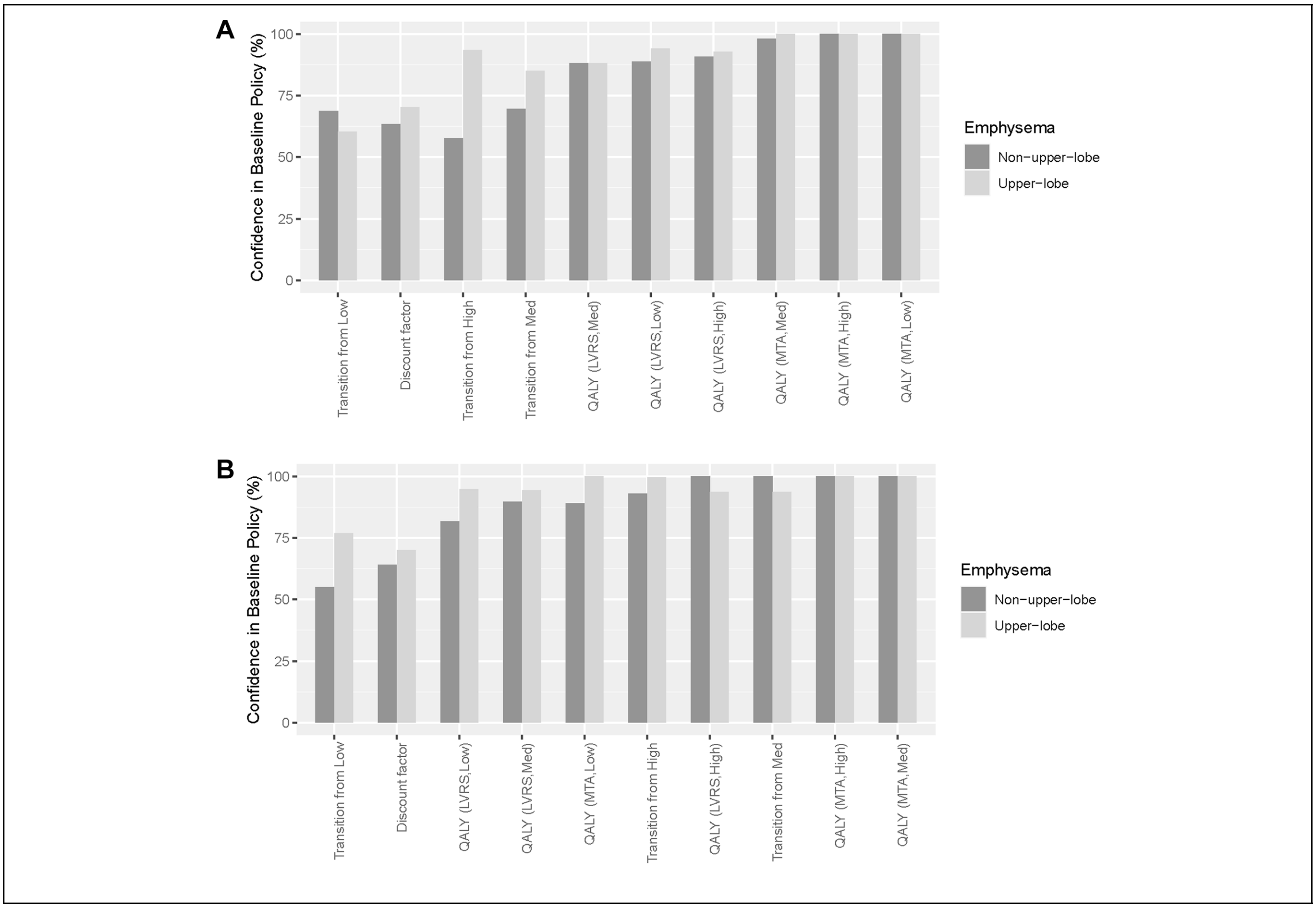

Figure 5 Univariate sensitivity analysis. (a) Maximum workload and (b) FEV_1 percent predicted as states for upper-lobe and non–upper-lobe emphysema.

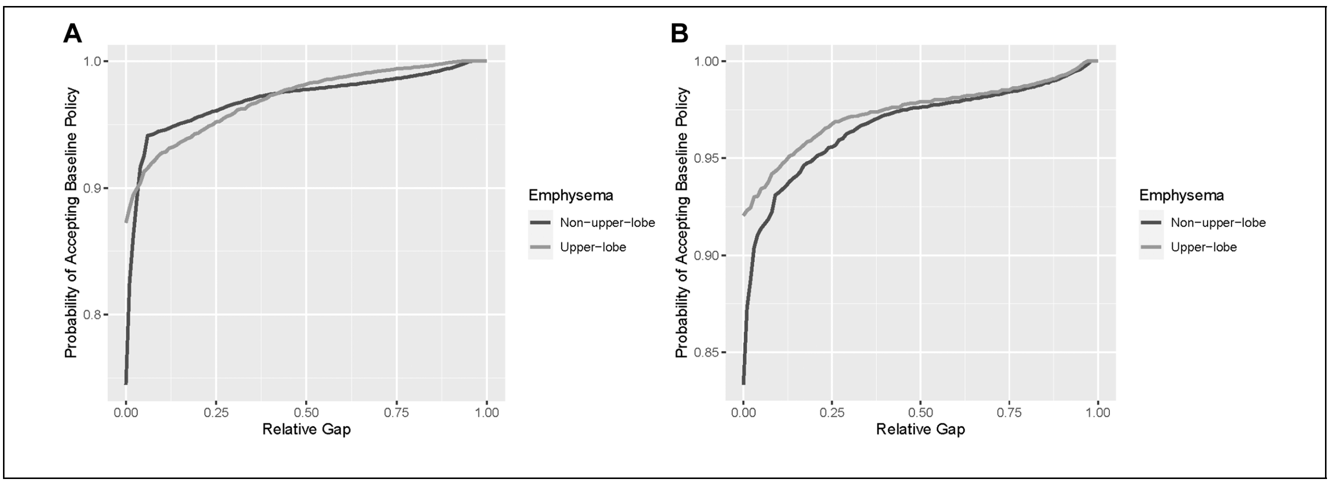

Figure 6 Multivariate sensitivity analysis. (b) FEV_1 percent predicted as states for upper-lobe and non–upper-lobe emphysema.

cases. The main difference between the 2 models is the age that the optimal decision changes from receiving LVRS to MTA. This is reasonable since the levels of maximum workload and FEV_1 are different in the 2 models. A possible future direction can be focusing on a model that the higher levels of maximum workload and FEV_1 are jointly considered as the states. Comparing the results of the joint model with the separate models that have the same levels for each measurement could provide more insights on the importance of the health states.

The QWB score was used to calculate the expected QALYs in the models. We noticed that the estimated expected QALYs was relatively small in comparison with the expected remaining life-years. The mean QWB score, for all patients in the NETT, was about 0.50 at the beginning, and it improved to 0.55 12 mo after the randomization. The outcome of a study[37] on quality-of-life scores confirmed that the mean QWB score, for the same patients, is relatively smaller compared with other scores such as the EQ-5D, SF-6D, and AQoL-8D. Their study indicated that QWB has greater content relating to pain, physical function, and vitality.

The discount factor is used to emphasize immediate rewards or the rewards that are expected to be gained in the next decision epochs. In all of the reported results, both cost and QALYs have been discounted by 97%, which is the standard rate practiced in the health policy literature.[38] In the sensitivity analysis, we examined the range of 0.95 to 0.99 as discount factor values and found the optimal decisions. Then, for each model, the age for which the optimal decision changes from LVRS to MTA was compared with the undiscounted model. Because discounting diminishes the value of expected QALYs when the chosen action is to continue medical treatment, a lower discount factor results in later ages favoring medical treatment over LVRS.

Estimating the transition probabilities was challenging because of the missing values and lack of data for some specific rare states. We used the maximum likelihood estimation method to estimate probabilities of transitioning from one state at a decision epoch to another state at the next decision epoch and the bootstrap method to find the confidence intervals. As observed in the results, the optimal action (i.e., the age to start LVRS) highly depends on the probability of transitioning to the death state. Thus, it is important to estimate this probability more accurately with more patient data.

This study has some data limitations. The main limitation is that the number of patients who participated in the NETT is not sufficient for decision modeling at the individual level. This restriction makes it challenging to reliably estimate the expected life-years, QALYs, and transition probabilities for each subgroup of patients. In addition, in the NETT, only 5 y of follow-up data are available for QWB, maximum workload, and FEV_1 values, which include some missingness as well. In this article, we demonstrated how to collect insights from limited clinical trial data. This facilitates an immediate analysis of quantifying the benefits of a treatment intervention compared with the control action in a sequential decision modeling framework, considering various patient characteristics.

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Supplemental Material

Supplementary material for this article is available on the *Medical Decision Making* website at http://journals.sagepub.com/home/mdm.

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