Quality-Adjusted Life Years and Costs of Mechanical Thrombectomy for Very Elderly Patients with Acute Ischaemic Stroke

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Keywords: very elderly, ischaemic stroke, mechanical thrombectomy, cost-effectiveness, incremental cost-effectiveness ratio

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Abstract

This study aimed to evaluate the cost-effectiveness of mechanical thrombectomy (MT) in patients aged 90 years and older with acute ischaemic stroke (AIS). We developed a cost-effectiveness model to compare MT with standard medical care (SMC) to SMC alone. The model, incorporating parameters for the effectiveness and costs of MT with SMC and SMC alone, was simulated until the cohort reached 100 years of age. The parameters were estimated from the prospective cohort study of the RESCUE-Japan Registry 2, claims databases, and published literature, with the perspective being Japan's public healthcare system. In the base-case model for an 8-year simulation period, the quality-adjusted life years (QALYs) for MT with SMC and SMC alone were 1.463 and 1.054 years, respectively. The expected costs were 14,553,772 Yen and 13,732,646 Yen, respectively. The incremental cost-effectiveness ratio (ICER) of MT with SMC compared to SMC alone was 2,009,744 Yen per QALY. A probabilistic sensitivity analysis showed a 66% probability that MT with SMC would be below the ICER threshold of 5,000,000 Yen per QALY. The cost-effectiveness analyses demonstrated that performing MT in addition to SMC for AIS in patients aged 90 years and older was acceptable from a cost-effectiveness perspective.

Keywords: very elderly, ischaemic stroke, mechanical thrombectomy, cost-effectiveness, incremental cost-effectiveness ratio

Introduction

Japan has been facing a rapid ageing of its population over the past few decades. According to the Statistics Bureau of the Ministry of Internal Affairs and Communications, the proportion of elderly individuals aged 65 years and older in the Japanese total population reached a record high of 29.1% (36.24 million people) in 2023, the highest in the world, with 2.63 million individuals aged 90 years and older.[1] In 2022, cerebrovascular diseases accounted for 6.9% (107,481 people) of total deaths in Japan, ranking fourth among all causes of death. Cerebral infarction was the most common form of cerebrovascular disease, affecting 59,363 people.[2] As the global population continues to age, it is anticipated that the number of elderly patients with stroke will increase.

There have been numerous studies on the efficacy and safety of mechanical thrombectomy (MT) for patients with acute ischaemic stroke (AIS) due to large vessel occlusion worldwide.[3] The cost-effectiveness of MT in addition to standard medical care (SMC) has been reported to be acceptable,[4] based on the DAWN[5] and DEFUSE 3 trials.[6] However, these studies targeted all patients without considering the very elderly population. A sub-analysis of the multicentre prospective study of the RESCUE-Japan Registry 2 demonstrated the usefulness of MT for patients with AIS aged 90 years and older.[7] Considering the limited life expectancy for such very elderly patients, the investigation of the cost-effectiveness of MT in those very elderly patients with AIS was clinically and politically relevant, especially in the super-ageing society.

Because no reports existed on the cost-effectiveness of MT for very elderly patients with AIS worldwide, we conducted a cost-effectiveness analysis of performing MT in addition to SMC for AIS patients aged 90 years and older within Japan's medical environment and healthcare system.

Materials and Methods

We conducted a cost-effectiveness analysis to compare MT with SMC and SMC alone in patients with AIS. The effectiveness was measured by quality-adjusted life years (QALYs) based on the Guideline for Preparing Cost-Effectiveness Evaluation to the Central Social Insurance Medical Council Version 3.0.[8)] The cost-effectiveness of MT with SMC was assessed by calculating the incremental cost-effectiveness ratio (ICER) compared to SMC alone. This study was approved by the Institutional Review Board of Hyogo Medical University (Approval number 4157). Informed consent was not applicable because all data were anonymously obtained from published papers and a claim database without individual identification.

All analyses were performed from a public healthcare perspective, and the analytic period was until the patient reached 100 years of age, which was sufficient time to observe nearly all patient's deaths. All costs and QALYs beyond the first year were discounted at an annual rate of 2% and converted to present value for the simulation. Model creation and analysis were performed using TreeAge Pro 2023 (TreeAge Software, Williamstown, MA, USA).

Model structure

In a sub-analysis of the RESCUE-Japan Registry 2 for patients aged 90 years and older, the MT with SMC group had a median age of 92 years (interquartile range: 90–94) with 82.2% being female, while the SMC alone group had a median age of 92 years (interquartile range: 91-94) with 77.6% being female.[7)] Therefore, we compared 2 initial treatment options for AIS patients aged 92 years: performing MT with SMC and SMC alone, including recombinant tissue-type plasminogen activator (rt-PA). The outcomes after the initial treatment were estimated according to the distribution of the modified Rankin Scale (mRS) score measured at 90 days after stroke. The mRS ranges from 0 to 6, with 0 representing no disability and 6 representing death.[9)]

We created a short-run decision analytic model (acute phase) to evaluate QALYs and costs within the first 3 months after stroke (Figure 1a). The patient cohort was then distributed into 3 health states based on the mRS score: 0–2, 3–5, and 6 (death). Subsequently, we used a long-run Markov model (chronic phase) to estimate the QALYs and cost for each 3-month cycle until patients reached 100 years of age (Figure 1b).

Probabilities

The probabilities of mRS 0–2, 3–5, and 6 (death) at 90 days after the onset of AIS for each treatment group were derived from the sub-analysis of the RESCUE-Japan Registry 2.[7)] As there was no available information on the transition probabilities between these statuses for Japanese patients, we applied the transition probabilities used in a UK study by Pizzo et al.[10)] into three-month cycles in the long-run Markov model (Table 1). We assumed that the probability of recurrent stroke was the same for patients with mRS 0–2 and with mRS 3–5, and patients could transition between mRS 0–2 and mRS 3–5 health states during the first year only; such transitions were not allowed after the second year of observation.[10)] After the second year, patients remained in the same state or transitioned to stroke recurrence or death. The all-cause mortality rates in the Markov model also reflected the Japanese Ministry of Health, Labour and Welfare's life tables.[11)]

Utilities

We estimated the utility values from a UK study by Pizzo et al.[10] because utility data for Japanese patients were unavailable. We set the values at 0.185 for mRS 0–2, 0.095 for mRS 3–5, and 0 for mRS 6 per three-month cycle, representing the quality of life associated with each mRS score over a three-month period (Table 1).

Costs and use of resources

We used claims data from DeSC Healthcare, Inc. (https://desc-hc.co.jp/en) to calculate the cost parameters in this study. The data were anonymised claims data from elderly patients aged 75 years and older insured under the late-stage elderly medical care system in Japan. We retrieved those with a diagnosis of cardiogenic cerebral embolism from April 1, 2018, to September 30, 2021. From 2,470 patients aged 90 years and older with a diagnosis of cardiogenic cerebral embolism (545 males, 1,925 females), we identified 48 patients who received MT with SMC during the acute phase of cerebral infarction and 64 patients who received SMC alone, excluding 2,241 patients who did not receive rt-PA treatment, 24 patients who did not have a diagnosis of cardiogenic cerebral embolism in the month they received rt-PA treatment and 93 patients without 3 consecutive months of claims data other than deaths (Figure 2). Among the 48 patients who received MT with SMC, 8 died within 3 months of treatment initiation, while among the 64 patients who received SMC alone, 11 died within 3 months of treatment initiation (Figure 2).

Since the claims data include standard treatment costs other than rt-PA, the cost for the 3-month acute phase was 4,190,065 Yen per patient for 40 survivors in the MT and SMC group and 3,026,095 Yen per patient for 8 dead. In the SMC alone group, the cost was calculated as 3,054,886 Yen per patient for 53 survivors and 1,728,073 Yen per patient for 11 dead. Because the costs stratified by mRS for survivors of acute stroke treatment over a 3-month period are not directly obtainable from the claims data, we indirectly calculated using the following method: The ratio of acute medical costs between mRS 0–2 and mRS 3–5 patients was reported as 1:1.58 by Shinohara et al.,[12] who conducted a medical economic analysis of strokes, detailing the acute medical expenses and annual caregiving costs by mRS score for Japanese patients. By adapting the ratio of acute medical costs for mRS 0–2 and mRS 3–5, weighted by the number of survivors from the sub-analysis of RESCUE-Japan 2,[7] we calculated the costs for mRS 0–2 and mRS 3–5. As a result, the acute cost for survivors over a 3-month treatment period was 2,919,906 Yen per patient for the MT with SMC group in mRS 0–2, and 4,613,451 Yen per patient in mRS 3–5. For the SMC alone group, the costs were 1,873,487 Yen per patient in mRS 0–2 and 2,960,110 Yen per patient in mRS 3–5.

The chronic phase costs after 3 months of treatment were calculated from the claims data as follows. Among the 40 patients who received MT with SMC and survived the acute phase of 3 months, 8 patients had consecutive claim data until 12 months (Figure 2). Among the 53 patients who received SMC alone and survived the acute phase, 24 patients had consecutive claim data until 12 months (Figure 2). From the claim data of survivors after 3 months, the cost for the 3-month chronic phase was obtained for both the MT with SMC and SMC groups, irrespective of mRS category. Because the costs by mRS category per 3-month period in the chronic phase were not directly obtainable from claims data, we indirectly calculated them using the following method. Based on the report of Shinohara et al.[12] on annual caregiving costs by mRS category for Japanese patients, we assumed a ratio of 1:6.91 for chronic phase medical costs between patients with mRS 0–2 and mRS 3–5. Next, we calculated the number of patients with mRS 0–2 and 3–5 from survivors of our SMC alone group at 4-6 months post-treatment, matching the proportions of survival, death, and recurrence calculated from the claims data for costs per 3-month period in the chronic phase. As a result, the costs per 3-month chronic phase period were estimated at 229,464 Yen per patient for mRS 0–2 and 1,585,598 Yen per patient for mRS 3–5. The cost for re-administration of rt-PA was calculated to 3,497,690 Yen. The costs and resources used in our model are presented in Table 1.

Sensitivity analysis

We conducted a probabilistic sensitivity analysis (PSA) to assess the uncertainties in the parameters that affected the cost-effectiveness. We assigned distributions to each parameter based on the levels of uncertainty around the deterministic values. The distributions assigned to each parameter are presented in Table 1. Random values were sampled from each distribution, and these values were used to calculate the results. This process was repeated in 10,000 simulations, generating 10,000 estimates for the cost and QALY of each treatment. Furthermore, the proportion of times each treatment exhibited higher benefits within the range of ICER thresholds was calculated. We used 5 million Yen/QALY as the ICER threshold, which was proposed to adjust the reimbursement of pharmaceutical and device products by Japan's cost-effectiveness evaluation system.[13)] We constructed cost-effectiveness acceptability curves (CEACs) to assess the effects of the ICER threshold.

Results

Base-case analysis

The base-case analysis up to 100 years of age per patient showed that the MT with SMC group yielded 1.463 QALYs at a total cost of 14,553,772 Yen, whereas the SMC alone group yielded 1.054 QALYs at a total cost of 13,732,646 Yen. The MT with SMC resulted in higher costs and more QALYs compared to SMC alone. The ICER was calculated to be 2,009,744 Yen/QALY (Table 2).

Sensitivity analysis

In the PSA results, 19.0% of iterations for the MT with SMC group were dominant, and 66.6% were considered cost-effective at the threshold of 5 million Yen per QALY (Figure 3a). The probabilities of cost-effectiveness of MT with SMC were consistently majority when the ICER threshold was 3,500,000 Yen/QALY or higher (Figure 3b).

Discussion

We showed that performing MT in addition to SMC for AIS in Japanese very elderly patients aged 90 years and older was cost-effective compared to SMC alone. The ICER was 2,009,744 Yen/QALY, which was below the 5 million Yen/QALY ICER threshold proposed to adjust the reimbursement of pharmaceutical and device products by Japan's cost-effectiveness evaluation system.[13)] The advantage of our research is that it is the first report to confirm the cost-effectiveness of MT in the Japanese healthcare system for patients aged 90 years and older with AIS using the results of the RESCUE-Japan Registry 2,[7)] a multicentre prospective study in Japan.

The ICER of MT in addition to SMC was reported as $662/QALY and $13,877/QALY based on the DAWN and DEFUSE 3 trials, respectively, which was within an acceptable range in the US, but the mean age of the cohort was 69.4 and 70 years in their models.[4)] Patil et al.[14)] also constructed a model of AIS with an average age of 67 years and the ICER of MT was below the ICER threshold in the US ($50,000/QALY). However, their sensitivity analysis revealed that ICER of MT was higher than the same ICER threshold and MT was not cost-effective when the age for stroke treatment was 82 years or older.[14)] A systematic literature review by Lim et al.[15)] also concluded that MT was not cost-effective compared to best medical management in AIS treatment for US patients aged 80 years and older, regardless of whether rt-PA treatment was used.

However, these studies were conducted in the US, and cost-effectiveness was affected by the healthcare system or population characteristics, which differed from other countries such as Japan. According to the 8th National Data Base Open Data from the Japanese Ministry of Health, Labor and Welfare,[16)] the number of MTs conducted for elderly patients in Japan during the 2021 fiscal year was 2,461 for patients aged 75-79 years, 2,864 for patients aged 80-84 years, 2,653 for patients aged 85–89 years, and 1,874 for patients aged 90 years and older. Our study reinforced that the decision to conduct the MT for very elderly patients could be considered acceptable from a cost-effectiveness perspective if the patients were eligible to receive MT. On the other hand, cost-effectiveness was one of the factors to justify the application of MT for the super-elderly population. The treating physicians had considered other factors to conduct or not conduct MT for such patients, including the individual patient's condition or preferences. While this study demonstrated the cost-effectiveness of MT in patients aged 90 years and older, the decision to conduct MT for individual patients should be carefully determined.

This study has several limitations. First, costs by mRS severity were not obtained directly from claims data. We thus estimated them based on indirect calculations, and the costs might not be accurate. Furthermore, due to the characteristics of claims data, it was difficult to fully extract information specific to ischaemic stroke treatment. Therefore, there was a possibility that the cost parameters may have been overestimated by including costs other than ischaemic stroke treatment. Second, utilities and transition probabilities of the model were quoted from a previous study in the UK because such data were not obtained from the Japanese cohort data. However, the utility values depend on the patient's condition regardless of the time from onset. In addition, we also assumed that the transition probabilities were common for those with the same mRS. Therefore, we should investigate to estimate these data of Japanese elderly AIS patients. Third, we assumed that the probability of recurrent stroke was the same for mRS 0–2 patients and mRS 3–5 patients, but the probability of recurrent stroke might be higher for more severe patients. In addition, actual practice might be different from the base-case scenario. Other situations, including best-case or worst-case scenarios, might happen. To account for these limitations, we conducted probabilistic sensitivity analyses, and the cost-effectiveness of MT with SMC had a 66% chance of being under the ICER threshold of 5 million Yen/QALY, which was the lowest value proposed in Japan. Therefore, the cost-effectiveness of MT was considered robust if other thresholds were applied. Fourth, we estimated the mRS distribution at 90 days after stroke was obtained from RESCUE-Japan Registry 2 in which endovascular therapy rather than MT was assessed. However, 88% of endovascular therapy in RESCUE-Japan Registry 2 was MT,[7)] and this study estimated the cost of MT, then we estimated the cost-effectiveness of MT assuming the efficacy of MT was similar to endovascular therapy. Fifth, our study was conducted from a public healthcare perspective and did not consider social costs such as public nursing care fees or caregiver productivity losses. If these costs were considered, the cost-effectiveness of MT could be higher. Finally, our cost-effectiveness analysis was conducted in the Japanese healthcare system and population, the generalisability of our findings is uncertain outside Japan. Because the cost-effectiveness reflects the local social environment, such cost-effectiveness analyses should be conducted locally.

In conclusion, our cost-effectiveness analysis demonstrated that performing MT in addition to SMC was cost-effective for very elderly Japanese patients with AIS aged 90 years and older. Further investigations should be necessary to predict which very elderly patients would benefit from MT. Such reliable stratification methods would improve the efficacy of MT as well as its cost-effectiveness.

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Conflicts of Interest Disclosure

Mr. Inaba is an employee of Takeda Pharmaceutical Company Limited. Dr. Morimoto reports lecturer's fees from Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Japan Lifeline, Pfizer, Tsumura and UCB; manuscript fee from Pfizer; advisory board for GlaxoSmithKline, Novartis and Teijin. Dr. Sakakibara and Dr. Uchida, who are members of the Japan Neurosurgical Society (JNS), have registered online self-reported Conflicts of Interest Disclosure Statement Forms via the website for JNS members.

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Table 1. List of input parameters

	Base-case value	Distribution	Range	Source
Probabilities at 90 days after the onset of AIS				
mRS 0-2 after MT with SMC	0.2	Dirichlet	0-1	7
mRS 3-5 after MT with SMC	0.63	Dirichlet	0-1	7
mRS 6 after MT with SMC	0.16	Dirichlet	0-1	7
mRS 0-2 after SMC alone	0.01	Dirichlet	0-1	7
mRS 3-5 after SMC alone	0.73	Dirichlet	0-1	7
mRS 6 after SMC alone	0.26	Dirichlet	0-1	7
Transition probabilities				
Movement from up to the end of year 1 to 3 months				
mRS 0-2				
mRS 0-2	0.955	Dirichlet	0-1	10
mRS 3-5	0.024	Dirichlet	0-1	10
Recurrent stroke	0.013	Dirichlet	0-1	10
mRS 6	0.008	Dirichlet	0-1	10
mRS 3-5				
mRS 3-5	0.919	Dirichlet	0-1	10
mRS 0-2	0.029	Dirichlet	0-1	10
Recurrent stroke	0.013	Dirichlet	0-1	10

mRS 6	0.039	Dirichlet	0-1	10
Movement from after year 1 to 3 months				
mRS 0-2				
mRS 0-2	0.979	Dirichlet	0-1	10
mRS 3-5	0	Dirichlet	0-1	10
Recurrent stroke	0.013	Dirichlet	0-1	10
mRS 6	0.008	Dirichlet	0-1	10
mRS 3-5				
mRS 3-5	0.948	Dirichlet	0-1	10
mRS 0-2	0	Dirichlet	0-1	10
Recurrent stroke	0.013	Dirichlet	0-1	10
mRS 6	0.039	Dirichlet	0-1	10
Recurrent stroke after MT with SMC				
mRS 0-2	0.867	Dirichlet	0-1	10
mRS 3-5	0.104	Dirichlet	0-1	10
mRS 6	0.029	Dirichlet	0-1	10
Recurrent stroke after SMC alone				
mRS 0-2	0.834	Dirichlet	0-1	10
mRS 3-5	0.137	Dirichlet	0-1	10
mRS 6	0.029	Dirichlet	0-1	10
Utilities per 3 months				
mRS 0-2	0.185	Beta	0-1	10
mRS 3-5	0.095	Beta	0-1	10

Recurrent stroke	0.087	Beta	0-1	10
mRS 6	0		0	10
Costs				
Acute costs first 3 months				
MT with SMC				
mRS 0-2 (Yen)	2,919,906	Gamma		12, Claims data.
mRS 3-5 (Yen)	4,613,451	Gamma		12, Claims data.
Acute event fatal stroke mRS 6 (Yen)	3,026,095	Gamma		12, Claims data.
SMC alone				
mRS 0-2 (Yen)	1,873,487	Gamma		12, Claims data.
mRS 3-5 (Yen)	2,960,110	Gamma		12, Claims data.
Acute event fatal stroke mRS 6 (Yen)	1,728,073	Gamma		12, Claims data.
Chronic costs every 3 months				
mRS 0-2 (Yen)	229,464	Gamma		12, Claims data.
mRS 3-5 (Yen)	1,585,598	Gamma		12, Claims data.

recurrent stroke (Yen)	3,497,690	Gamma	12, Claims data.

AIS: acute ischemic stroke; mRS: modified-Rankin-Scale; MT: mechanical thrombectomy; SMC: standard medical care.

Table 2. Base case cost-effectiveness analysis

Treatment	Total cost (Yen)	Incremental cost (Yen)	Life expectancy (QALY)	Incremental effectiveness (QALY)	ICER (Yen/QALY)
SMC alone	13,732,646		1.054		
MT with SMC	14,553,772	821,126	1.463	0.408	2,009,744

ICER: incremental cost-effectiveness ratio; MT: mechanical thrombectomy; QALY: quality-adjusted life-years; SMC: standard medical care.

Figure Legend

Figure 1. (a) Short-run analytic model (first 3 months after stroke). (b) Long-run Markov model. The decision model consists of a short-run analytic model and a long-run Markov model. Patients receive either mechanical thrombectomy with standard medical care or standard medical care alone as acute treatment and enter a health state of the modified Rankin Scale (mRS) after the 3-month acute phase. Patients who survive the acute phase enter the Markov model, which runs in 3-month cycles. After every 3 months, patients can remain in their current mRS state, transition to another mRS state, experience a recurrent stroke, or die. After a recurrent stroke, patients either transition to mRS 0-2, mRS 3-5 or die. Note that standard medical care also includes recombinant tissue-type plasminogen activator.

A square indicates a decision node, in this case, the decision to treat with either mechanical thrombectomy with standard medical care or standard medical care alone. Circles indicate chance nodes. Circles with the letter M indicate Markov nodes. Triangles indicate terminal nodes.

Figure 2. Flowchart of the patient selection for cost parameters.

Figure 3. (a) Monte Carlo simulations of incremental cost and incremental quality-adjusted life years (QALY).

The results are shown as scatterplots of incremental costs and incremental QALYs of mechanical thrombectomy with standard medical care compared with standard medical care alone per patient with acute ischaemic stroke. Each dot represents one simulation result. The black line indicates the ICER threshold of 5,000,000 Yen per QALY. The number of blue dots below the black line represents the probability for mechanical thrombectomy with standard medical care to be cost-effective at the ICER threshold of 5,000,000 Yen per QALY.

(b) Cost-effectiveness acceptability curves (CEACs)

The curves show the probability of whether the mechanical thrombectomy with the standard medical care group or the standard medical care alone group is cost-effective at various ICER thresholds. The dotted line shows the ICER thresholds used in Japan's cost-effectiveness evaluation system.
ICER: incremental cost-effectiveness ratio.

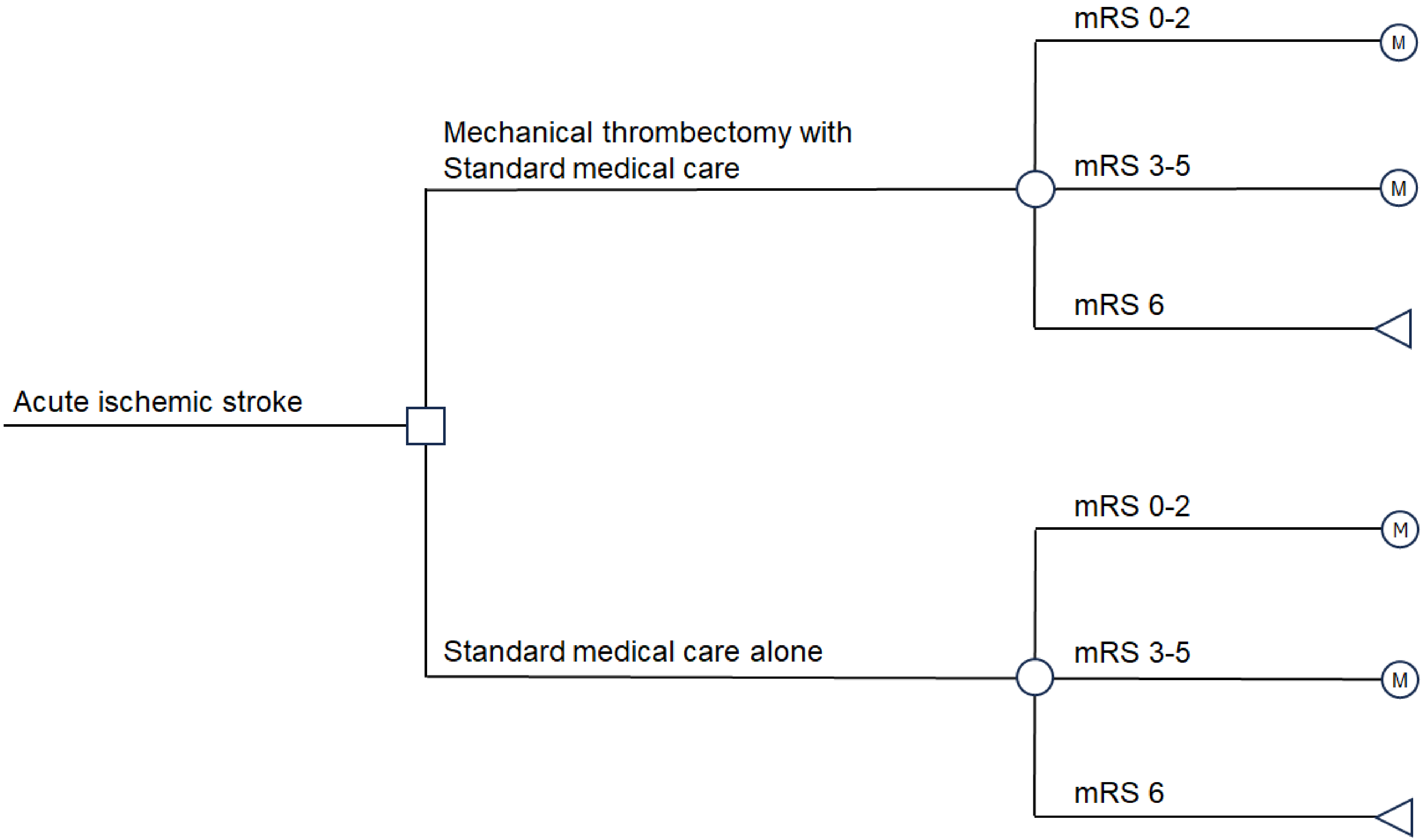

Figure 1. (a) Short-run analytic model (first three months after stroke).

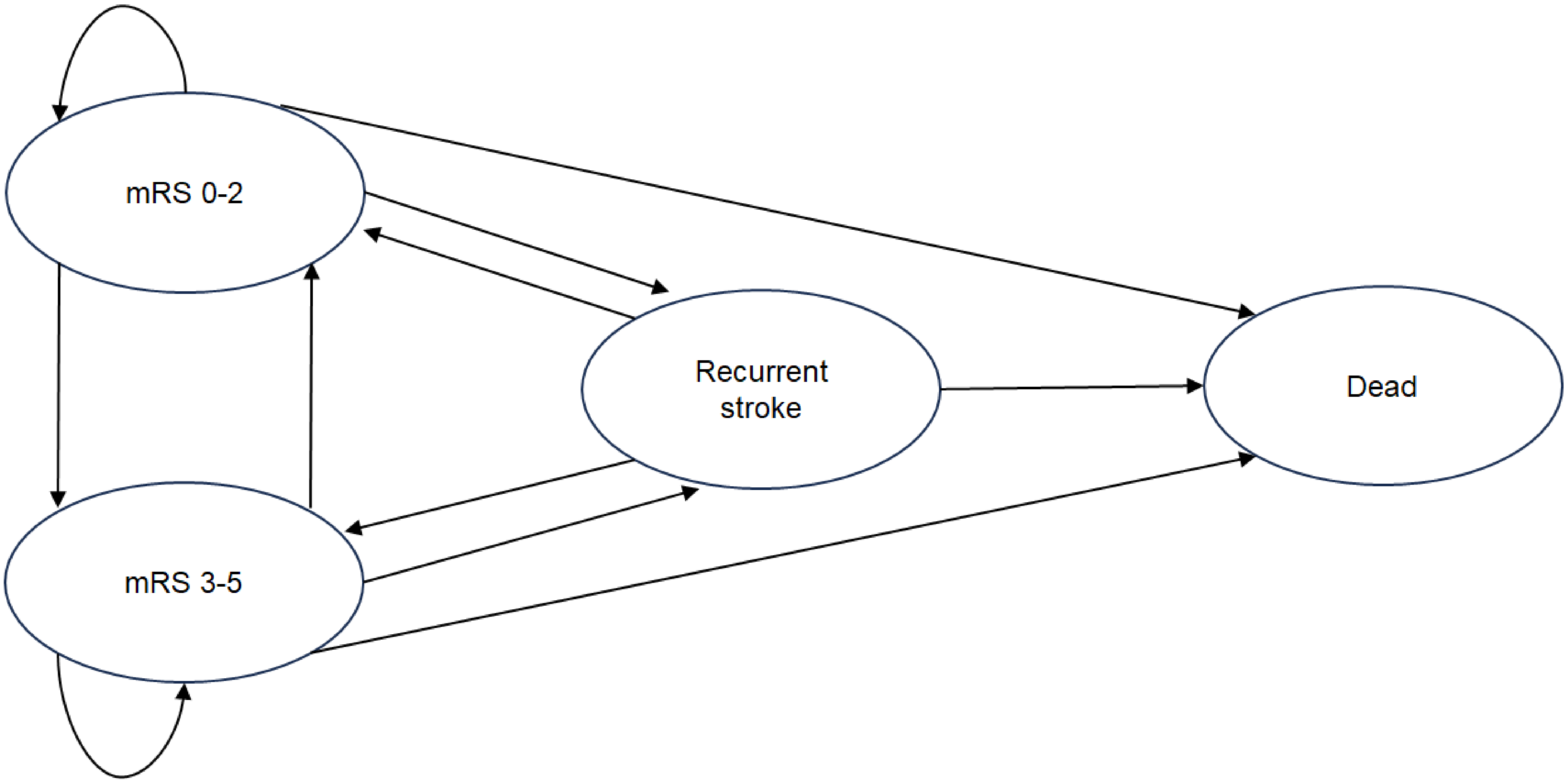

Figure 1. (b) Long-run Markov model.

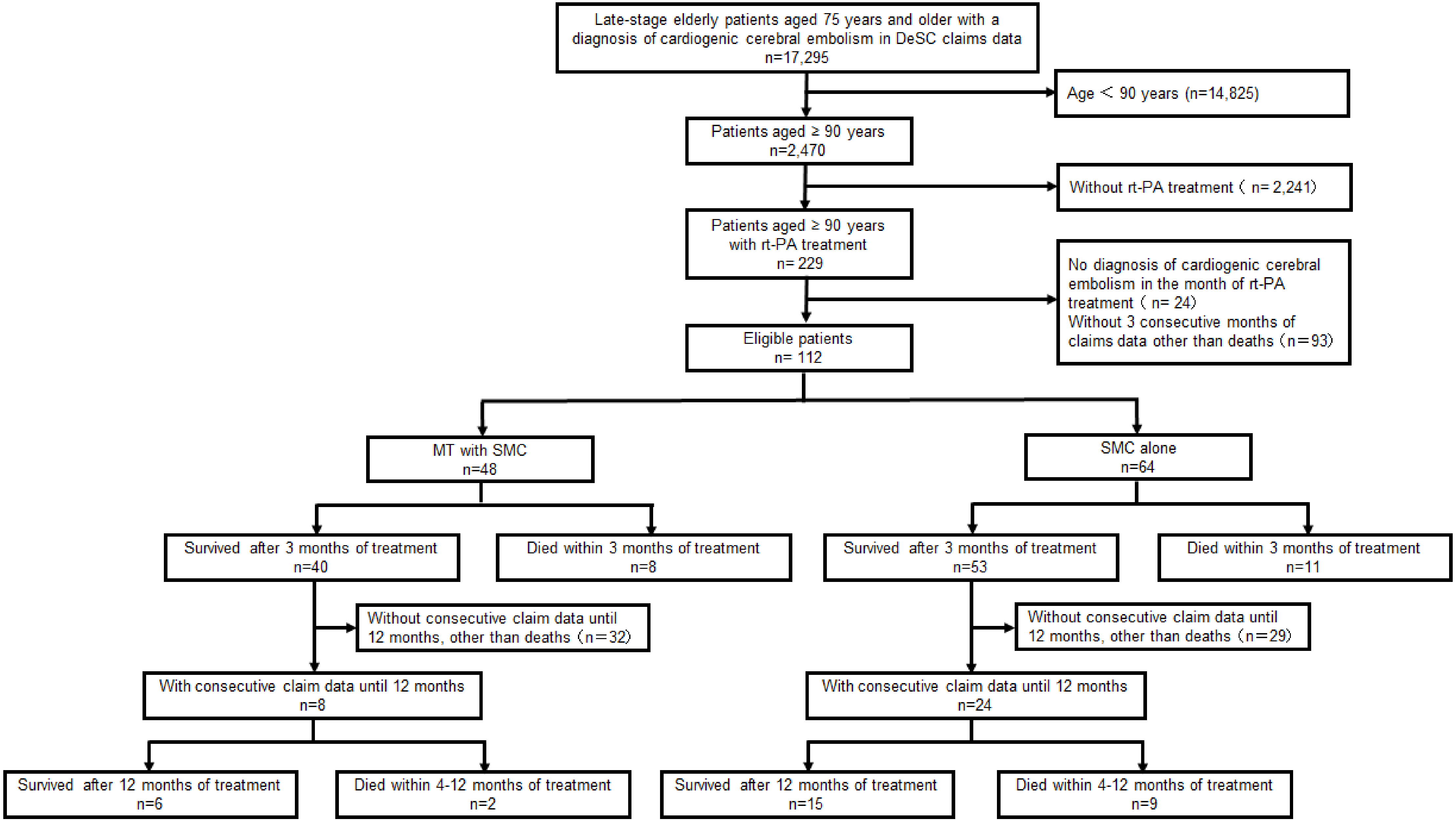

Figure 2. Flowchart of the patient selection for cost parameters.

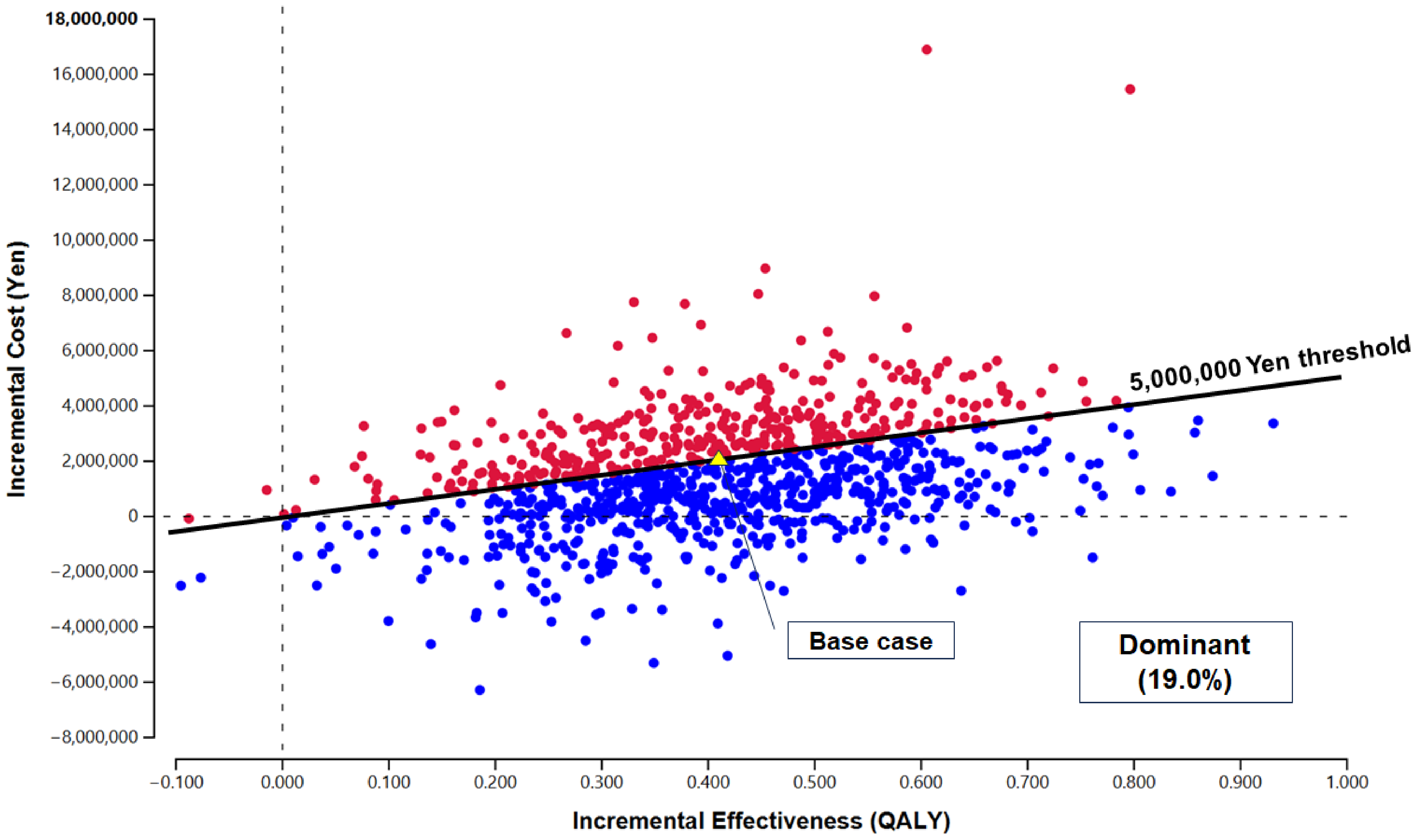

Figure 3. (a) Monte Carlo simulations of incremental cost and incremental quality-adjusted life-years (QALY).

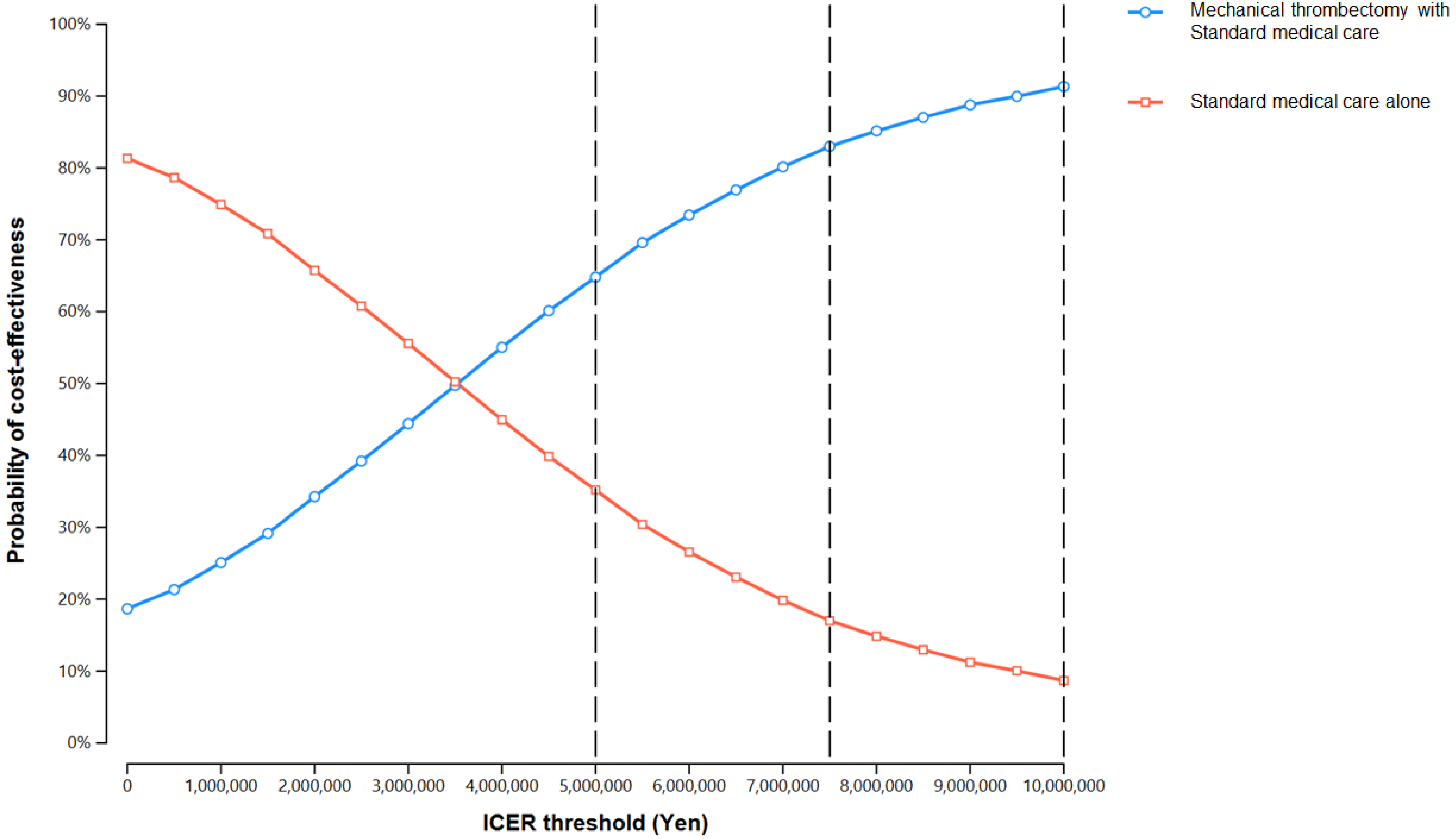

Figure 3. (b) Cost-effectiveness acceptability curves (CEACs).