



Original Article

# Surgical revascularization for Moyamoya disease in the United States: A cost-effectiveness analysis

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**Objective:** Moyamoya disease (MMD) is a vasculopathy of the internal carotid arteries with ischemic and hemorrhagic sequelae. Surgical revascularization confers upfront peri-procedural risk and costs in exchange for long-term protective benefit against hemorrhagic disease. The authors present a cost-effectiveness analysis (CEA) of surgical versus non-surgical management of MMD.

**Methods:** A Markov Model was used to simulate a 41-year-old suffering a transient ischemic attack (TIA) secondary to MMD and now faced with operative versus non-operative treatment options. Health utilities, costs, and outcome probabilities were obtained from the CEA registry and the published literature. The primary outcome was incremental cost-effectiveness ratio which compared the quality adjusted life years (QALYs) and costs of surgical and nonsurgical treatments. Base-case, one-way sensitivity, two-way sensitivity, and probabilistic sensitivity analyses were performed with a willingness to pay threshold of \$50,000.

**Results:** The base case model yielded 3.81 QALYs with a cost of \$99,500 for surgery, and 3.76 QALYs with a cost of \$106,500 for nonsurgical management. One-way sensitivity analysis demonstrated the greatest sensitivity in assumptions to cost of surgery and cost of admission for hemorrhagic stroke, and probabilities of stroke with no surgery, stroke after surgery, poor surgical outcome, and death after surgery. Probabilistic sensitivity analyses demonstrated that surgical revascularization was the cost-effective strategy in over 87.4% of simulations.

**Conclusions:** Considering both direct and indirect costs and the postoperative QALY, surgery is considerably more cost-effective than non-surgical management for adults with MMD.

**Keywords** Cost-effectiveness, Moyamoya disease, Cerebrovascular neurosurgery, Surgical revascularization, Stroke

## INTRODUCTION

Moyamoya disease (MMD) is a chronic, progressive vasculopathy of the internal carotid arteries that may cause hemorrhagic and ischemic stroke.<sup>1)</sup> This vasculopathy disproportionately affects women and people of Asian descent.<sup>9)19)</sup> Surgical interventions for MMD include direct bypass using the superficial temporal artery anastomosed to the middle cerebral artery (extracranial-intracranial [EC-IC] bypass), or indirect bypass such as encephaloduroarteriosynangiosis in which the superficial temporal artery is placed on the dural surface allowing angiogenesis to revascularize the cerebral cortex.<sup>1)</sup>

The surgical goal of cerebral revascularization is to prevent progression of symptomology, alleviate intracranial hemodynamic stress, and reduce the incidence of subsequent ischemic or hemorrhagic stroke.<sup>7)11)14)25)34)</sup> Miyamoto et al. performed the first randomized, multicenter prospective trial that investigated the difference in hemorrhagic stroke rate between adult patients that received surgical revascularization and those that did not, finding that surgery was associated with a diminished rate of hemorrhagic stroke.<sup>21)</sup> Liu et al. conducted a retrospective analysis assessing surgical revascularization in adult Moyamoya patients presenting with hemorrhage and similarly found reduced subsequent hemorrhagic stroke, superior neurologic outcomes, and improved rates of returning to work compared to conservative management.<sup>17)</sup> However, surgical revascularization is associated with increased inpatient costs and upfront periprocedural risks of stroke or neurologic deficit.<sup>13)</sup> Markov models have been increasingly utilized by clinicians to model the relative cost-effectiveness of treatment decisions.<sup>30)</sup> To this end, model inputs include both direct and indirect costs, utility of health state (a number between 0 and 1), and probability of health outcomes. Competing treatment decisions are evaluated for differences in quality adjusted life years (QALYs), which is a scalar multiple of years living and utility, and lifetime cost of a treatment decision. This difference is captured by the incremental cost-effectiveness ratio (ICER). To

date, no formal assessment of the possible cost-effectiveness of surgical revascularization for MMD has been performed and within this study, we present the first decision analytic Markov Model to calculate the long-term health utility and economic impact of surgical revascularization versus conservative management in patients with MMD.<sup>30)</sup>

## MATERIALS AND METHODS

### Treatment strategies

Our decision model captures the management decision for a 41-year-old female with MMD who has been admitted to a hospital in the United States with a first hemorrhagic episode and is now considering surgical revascularization or conservative management. This age, gender, and symptomology was chosen to represent the patient population described in the prospective randomized trial by Miyamoto et al.<sup>21)</sup> The competing treatment strategies are listed below:

Strategy 1: Surgical revascularization after admission for MMD

Strategy 2: Nonsurgical management after admission for MMD

### Decision model

Surgical revascularization was defined as direct bypass and conservative management included nonsurgical treatment strategies.<sup>21)</sup> Model inputs such as surgical success rates, cost, neurologic outcomes, and rates of subsequent major stroke were derived from available published literature placing emphasis on randomized, multicenter prospective data when possible. QALYs were used to model long-term health utility. QALY values range between 0 (death) and 1 (a year of life at full health).

The base-case model simulates outcomes for a 41-year-old female patient with MMD and includes age-specific risk of death from other non-cerebrovascular causes derived from the Centers of Disease Control and Prevention mortality data.<sup>4)17)</sup> A basic form of

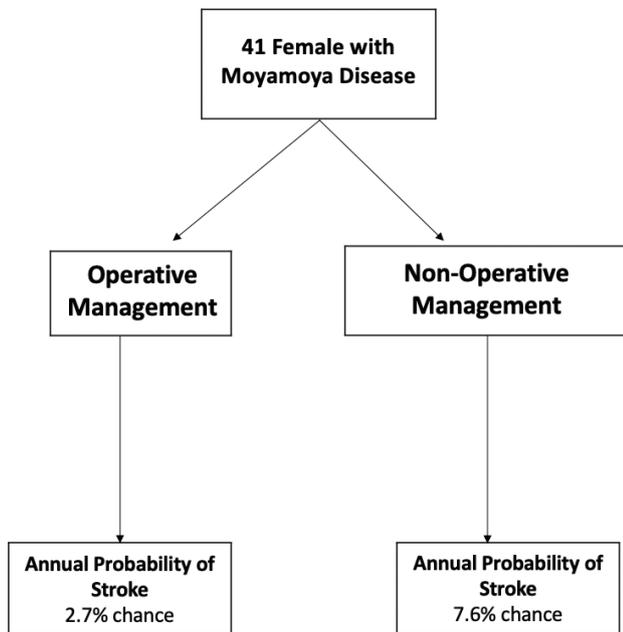
the decision analysis model is illustrated in Fig. 1. The 5-year and lifetime cost-effectiveness after surgical are calculated.

**Model inputs**

*Neurologic outcomes and health utilities*

The modified Rankin Scale (mRS) score was used to define neurologic outcome. Scores were grouped for analysis: 0-2 (good functional and neurologic outcome), 3-5 (poor functional and neurologic outcome), and 6 (death).<sup>31)</sup> Using techniques described elsewhere, mRS scores were converted into QALYs.<sup>24)</sup>

Good neurologic outcome was associated with 0.85 QALYs/year, poor neurologic outcome was associated with 0.48 QALYs/year, and death was defined as 0 QALYs/year.<sup>24)31)</sup> Complications associated with surgical revascularization or conservative treatment were incorporated as diminished mRS scores resulting in greater rehabilitation costs or neurologic disability. Health utilities along with model probabilities described below are fully listed in Table 1.



**Fig. 1.** Markov modeling decision tree of a 41-year-old female with transient ischemic attack due to Moyamoya disease. The patient can either undergo surgery or be observed with no treatment. The outcomes associated with surgery and no surgery are listed, including the annual risk of stroke. The probabilities and health utilities for each respective outcome are also included.

**Model probabilities**

*Neurologic outcome*

Probabilities of each neurologic outcome for respective treatment strategies were derived from existing values available within the published literature.<sup>13)17)</sup> Guzman et al. found that of 264 patients undergoing direct revascularization for MMD, 95.7% were discharged with minimal or minor neurologic deficit (mRS Score 0-2), 3.5% were discharged with a major neurologic deficit (mRS Score 3-5), and 0.75% of patients died.<sup>9)</sup> Similarly, Starke et al. found that only 1 in 390 patients (0.25%) sustained a fatal complication of direct bypass during admission.<sup>26)</sup> These findings were similar to other reported morbidity and mortality rates after direct bypass for MMD from smaller studies further strengthening the consistency of this model input.<sup>10)</sup> Given that Guzman et al.<sup>9)</sup> was the largest prospective study reporting neurologic outcomes as defined by mRS after bypass surgery for MMD, these values were incorporated within our model.

*Hospitalization and major stroke*

Miyamoto et al. reported rates of major stroke (hemorrhage) as 2.7% and 7.6% in the revascularization and non-revascularization cohorts, respectively.<sup>21)</sup> Given that nearly half of all patients who have adult-onset MMD present with hemorrhage,<sup>28)</sup> we chose to use Miyamoto's study to model the quantitative risk of re-bleeding for patients that underwent surgery or non-operative management.

Using data from the National Inpatient Sample, Kainth et al. showed that Moyamoya patients sustaining hemorrhagic stroke had a 46.2% chance of being discharged with only minimal disability (mRS Score 0-2), 35.4% chance of being discharged with major disability (mRS Score 3-5), and 18.2% chance of death.<sup>13)</sup> Utilizing population based data by Luengo-Fernandez et al., our model assumed that patients with major disability had a one-year mortality rate of 60%.<sup>18)</sup> Our model also assumed that patients with baseline poor neurologic status who sustained an additional hemorrhagic stroke had a 63% chance of remaining at poor neurologic status or a 37% of death.<sup>8)</sup>

**Table 1.** Model probabilities, health utilities, patient characteristics, and direct and indirect costs incorporated within the model

Variable	Value	STD	Distribution	First author
Patient age	41	11.3	Binomial	Miyamoto et al. <sup>21)</sup>
<b>Clinical outcome probabilities</b>				
Good outcome (mRS Score 0-2) after initial revascularization	95.7%	19%	Beta	Guzman et al. <sup>9)</sup>
Poor outcome (mRS Score 3-5) after initial revascularization	3.5%	0.7%	Beta	Guzman et al. <sup>9)</sup>
Death after initial revascularization	0.75%	0.15%	Beta	Guzman et al. <sup>9)</sup>
Good outcome (mRS Score 0-2) after initial nonsurgical management	100	0	Beta	Kainth et al. <sup>13)</sup>
Annual probability of hemorrhagic stroke after revascularization	2.7%	0.54%	Beta	Miyamoto et al. <sup>21)</sup>
Annual probability of hemorrhagic stroke without revascularization	7.6%	1.52%	Beta	Miyamoto et al. <sup>21)</sup>
Good outcome (mRS Score 0-2) after stroke with good mRS baseline	46.2%	9.2%	Beta	Kainth et al. <sup>13)</sup>
Poor outcome (mRS Score 3-5) after stroke with mRS score 0-2 baseline	35.4%	7.1%	Beta	Kainth et al. <sup>13)</sup>
Death after stroke with (mRS Score 0-2) baseline	18.2%	3.6%	Beta	Kainth et al. <sup>13)</sup>
Poor outcome (mRS Score 3-5) after stroke with mRS Score 3-5 baseline	63%	12.6%	Beta	Grysiewicz et al. <sup>8)</sup>
Death after stroke with mRS score 3-5 baseline	37%	7%	Beta	Grysiewicz et al. <sup>8)</sup>
First year mortality rate with baseline mRS Score 3-5	60%	12%	Beta	Luengo-Fernandez et al. <sup>18)</sup>
<b>Health utilities (QALYs)</b>				
Good functional status mRS (0-2)	0.85	0.18	Beta	Rivero-Arias et al., <sup>24)</sup> Wali et al. <sup>31)</sup>
Poor functional status mRS (3-5)	0.48	0.24	Beta	Rivero-Arias et al., <sup>24)</sup> Wali et al. <sup>31)</sup>
Death mRS 6	0	0	Beta	Rivero-Arias et al., <sup>24)</sup> Wali et al. <sup>31)</sup>
<b>Costs (2018 Dollars)</b>				
Cost of initial admission with concurrent revascularization	\$75,804	\$625	Gamma	Titsworth et al. <sup>29)</sup>
Cost of initial admission without concurrent revascularization	\$51,472	\$759	Gamma	Titsworth et al. <sup>29)</sup>
Cost of subsequent hemorrhagic stroke admission	\$144,948	\$22,757	Gamma	Kainth et al. <sup>13)</sup>
Rehabilitation costs with good functional status mRS (0-2)	\$1,318	\$263	Gamma	Nelson et al., <sup>22)</sup> Wali et al. <sup>31)</sup>
Rehabilitation costs with poor functional status mRS (3-5)	\$15,174	\$3,034	Gamma	Nelson et al., <sup>22)</sup> Wali et al. <sup>31)</sup>

STD, standard deviation; mRS, modified Rankin Scale; QALYs, quality-adjusted life years

*Direct and indirect costs*

Titsworth et al. found that, in the Kids Inpatient Database, cost for pediatric hospital admission with revascularization at a high volume center was \$88,101 compared to \$62,509 without revascularization.<sup>29)</sup> As complex vascular neurosurgery increasingly takes place in regionalized centers, our model used Titsworth's cost of admission with revascularization to capture the cost of a stroke admission with surgical intervention. Kainth et al. found that hospital admissions for hemorrhage with MMD cost \$133,754 on average using the

Nationwide Inpatient Sample.<sup>13)</sup> The data provided by Kainth et al.<sup>13)</sup> was used to describe the costs associated with subsequent admissions for stroke related to MMD. These values were placed within our Markov Model to capture direct costs associated with hospital admission for MMD and hemorrhagic stroke.

Indirect costs associated with functional disability and long term rehabilitation associated with neurologic deficit were derived from prior cost-effectiveness studies based on rehabilitation and special nursing facility costs associated with each mRS score.<sup>22)31)</sup> All retrospectively

obtained costs were converted to 2018 US dollars to adjust for inflation.<sup>3)</sup> All cost information can be found in Table 1.

### Analysis

TreeAge Pro 2018 (TreeAge Software Inc., Williamstown, MA, USA) was used to construct our decision analysis Markov Model. This model discounted utilities and costs by 3% annually, a standard convention utilized in health economics research.<sup>12)</sup> The ICER, which calculates the difference in costs between the two treatment strategies divided by the difference in QALYs between the treatment arms, was used to determine cost-efficacy. Results from this model were considered cost-effective if the ICER yielded was less than a willingness to pay (WTP) threshold of \$50,000/QALY gained—a standard convention used in cost-effectiveness analyses.<sup>2)</sup> A treatment strategy was considered dominant if it yielded an outcome that generated more QALY for less total cost. All costs within this model are presented from a societal viewpoint.

The following analytic metrics are included within this model: the base-case analysis, one-way sensitivity analysis, two-way sensitivity analysis, and probabilistic sensitivity analysis. The base-case analysis refers to the outputs generated from our Markov model using each model input derived from the best available input estimation from the published literature. To account for uncertainty in the true value of model inputs and potential limitations to the model inputs that were utilized, we augmented our analysis with a one-way and two-way sensitivity analyses to demonstrate how a range of model inputs may influence cost-efficacy. The probabilistic sensitivity analysis was also performed to address model input uncertainty and utilized a Monte Carlo simulation across 100,000 iterations which sampled model inputs along with standard deviations for each model input.<sup>5)</sup> Standard deviations were collected from the literature whenever possible, and otherwise were assumed to be 20% of the mean value of the model input, a standard practice in cost-effectiveness modeling.<sup>30)31)</sup>

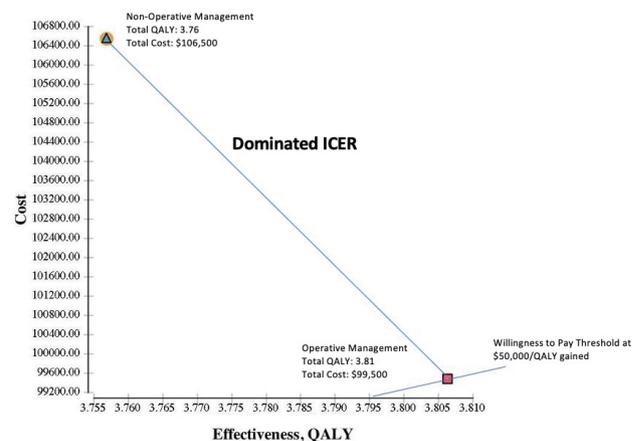
## RESULTS

### Base-case analysis

The base-case analysis across five years demonstrated that surgical revascularization was associated with 3.81 QALYs at a total cost of \$99,500 while conservative management resulted in 3.76 QALYs at a total cost of \$106,500 (Fig. 2). This resulted in an increase in .05 QALYs and saving of \$7,000 with surgery compared to management over the first initial five years. Surgery yielded greater QALYs while having less cost, which demonstrates that it was not only cost-effective but also the dominant strategy. When modeled across a lifetime, the surgical revascularization treatment arm yielded 14.80 QALY at a lifelong cost of \$171,200 while conservative management yielded 11.39 QALY at a lifelong cost of \$224,600. Over a lifetime, surgical revascularization saved \$53,400 and yielded 3.41 additional QALYs, further demonstrating that surgical revascularization remained a cost-effective and dominant strategy.

### One-way sensitivity analysis

Across a five year period, the one-way sensitivity analysis demonstrated that our cost-effectiveness model was



**Fig. 2.** Illustration of base case model. No treatment yields QALY of 3.76 at cost of \$106,500 and surgical revascularization yields QALY of 3.81 at cost of \$99,500. Surgery dominates no treatment with an increase in QALY of .05 and decrease in cost of \$7,000. The WTP threshold is included to demonstrate the QALY and cost of interventions considered cost effective with respect to surgery. QALY, quality-adjusted life years; WTP, willingness-to-pay; ICER, incremental cost-effectiveness ratio.

most sensitive to: 1) cost of revascularization surgery of \$85,000 above which no treatment is more cost effective, 2) annual probability of stroke of 6.3% with conservative management after which surgery is more cost effective, 3) annual probability of stroke after revascularization of 4.2% after which no surgery is more cost effective, 4) cost of admission for hemorrhagic stroke of \$112,000 after which surgery is more cost effective, 5) probability of poor surgical outcome with surgery of 12.5% above which no surgery is more cost effective, and 6) probability of death after surgery of 9.0% after which no treatment is more cost effective Table 2.

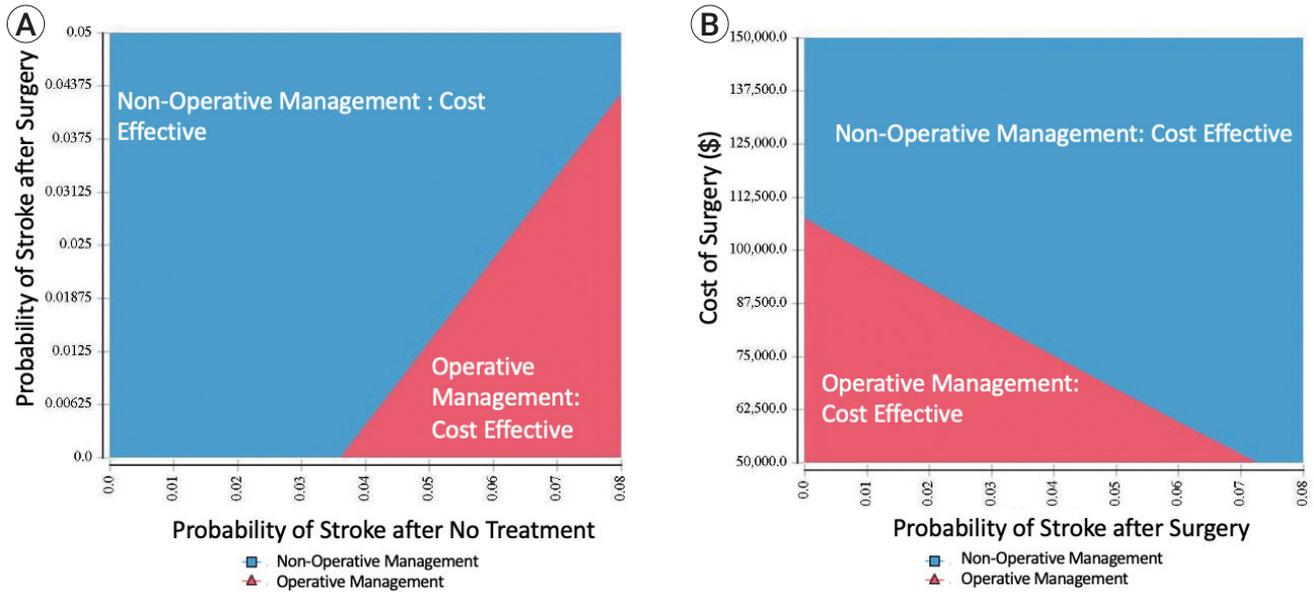
### Two-way sensitivity analysis

A two-way sensitivity analysis was constructed to determine the cost-effective strategy as two variables change concurrently and all other variables remain constant. When evaluating the cost and risk of perioperative stroke, surgery remained the cost-effective strategy if the probability of perioperative stroke was less than 7% and the cost of surgery was less than \$105,000 (Fig. 3). When comparing the risk of stroke with or without surgery, surgical revascularization for Moyamoya remained the cost-effective strategy if the probability of stroke without surgery was greater than 3.6% and the probability of

**Table 2.** One-way sensitivity analysis demonstrating changes in ICER

Parameter	Value used for sensitivity analysis	ICER across 5 years (\$/QALY gained)	ICER across lifetime (\$/QALY gained)
Cost of surgical revascularization	\$50,000	D \$664,170.32	D \$22,657.93
	\$70,000	D \$260,043.59	D \$16,934.22
	\$90,000	\$144,083.14	D \$11,210.52
	\$110,000	\$548,209.87	D \$5,486.81
	\$130,000	\$952,336.60	\$236.90
	\$150,000	\$1,356,463.33	\$5,960.60
Probability of stroke after conservative management	0.0%	D \$234,278.66	D \$22,658.74
	1.0%	D \$237,271.50	D \$23,720.47
	2.0%	D \$242,275.56	D \$27,186.17
	3.1%	D \$251,417.63	D \$69,524.00
	4.1%	D \$271,473.09	D \$5,978.31
	5.1%	D \$341,867.99	D \$12,580.44
Probability of stroke after surgical revascularization	0%	D \$191,285.12	D \$17,739.35
	1.6%	D \$173,436.52	D \$16,449.53
	3.2%	D \$110,277.13	D \$14,581.71
	4.8%	D \$504,594.23	D \$10,645.77
	6.4%	D \$276,129.55	\$14,406.01
	8.0%	D \$247,803.00	D \$35,326.16
Cost of hemorrhagic stroke admission	\$100,000	\$51,886.92	D \$8,284.45
	\$130,000	D \$78,031.83	D \$12,171.58
	\$160,000	D \$207,950.58	D \$16,058.72
	\$190,000	D \$337,869.33	D \$19,945.85
	\$220,000	D \$467,788.08	D \$23,832.98
	\$250,000	D \$597,706.83	D \$27,720.11
Probability of poor outcome (mRS Score 3-5) after surgery	2.8%	D \$111,392.10	D \$14,774.20
	3.5%	D \$142,766.01	D \$15,273.20
	4.2%	D \$199,486.58	D \$15,791.64
	4.9%	D \$333,085.96	D \$16,330.67
	5.6%	D \$1,028,517.95	D \$16,891.55
	6.3%	\$928,266.37	D \$17,475.62
Probability of death after surgery	.25%	D \$107,955.77	D \$14,836.46
	.50%	D \$123,132.35	D \$15,053.20
	.75%	D \$142,766.01	D \$15,273.20
	1.0%	D \$169,158.16	D \$15,496.55
	1.25%	D \$206,524.01	D \$15,723.33
	1.5%	D \$263,504.08	D \$15,953.60

mRS, modified Ranking scale; ICER, incremental cost-effectiveness ratio  
D, surgery dominated observation; not a true ICER  
D, observation dominated surgery; not a true ICER

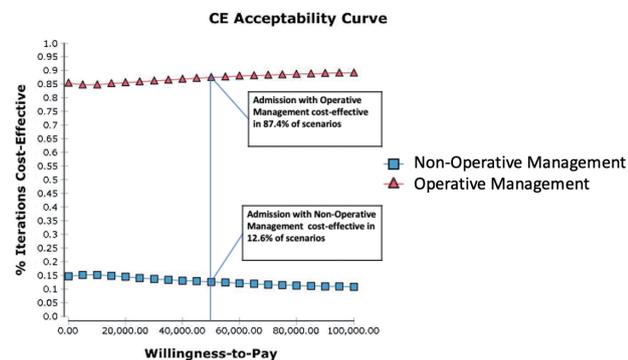


**Fig. 3.** (A) Two-way Sensitivity Analysis: Probability of Stroke after Surgery vs. Probability of Stroke without Surgery (B) Probability of Stroke after Surgery vs. Cost of Surgery. Surgery is cost-effective when the probability of stroke was less than 3.8% with surgery and greater than 3.6% without surgery. Surgery is cost-effective when the probability of stroke was less than 7% with surgery and the cost of surgery was less than \$105,000.

stroke with surgery was less than 3.8%.

**Probabilistic sensitivity analysis (Fig. 4)**

A Monte Carlo probabilistic sensitivity analysis was constructed utilizing 100,000 iterations across all distributions of input variables. This model demonstrated that surgical revascularization was the dominant cost-effective strategy. At the pre-defined WTP threshold of \$50,000 per QALY gained, surgical revascularization was the cost-effective strategy in 87.4% of the 100,000 iterations.



**Fig. 4.** Cost-effectiveness acceptability curve demonstrates that at WTP threshold of \$50,000, surgery is cost-effective in 87.4% of iterations. WTP, willingness-to-pay.

**DISCUSSION**

Numerous studies have investigated the likelihood of hemorrhagic and ischemic stroke following surgical or conservative management of MMD.<sup>32)</sup> There is strong evidence to support surgical revascularization for prevention of these long-term sequelae.<sup>27)</sup> However, surgery involves upfront costs and perioperative risks including stroke. Our study is the first to quantify the quality of life impact and health costs associated with surgical revascularization when compared with conservative management. Our model demonstrates that revascularization is cost-effective across a five-year horizon by yielding 3.81 QALYs with a cost of \$99,500 in comparison to nonsurgical treatment with 3.76 QALYs and a cost of \$106,500.

Our model was sensitive to several key assumptions such as cost of surgery, probability of stroke without surgery, probability of stroke after surgery, cost of admission for hemorrhagic stroke, probability of poor surgical outcome, and probability of death after surgery. The two-way sensitivity analysis demonstrated that operative

management was superior to observation when annual probability of stroke without surgical revascularization was greater than 3.6% or when risk of stroke with surgery remained less than 3.8%. These findings provide parameters that can help evaluate specific institutions' ability to provide safe and cost-effective surgical revascularization. There is a growing nationwide emphasis on centralization of surgical care as it pertains to complex cerebrovascular disorders.<sup>20)</sup> Existing data demonstrate that high volume centers are associated with improved clinical outcome and reduced health care costs for surgical revascularization for MMD.<sup>29)</sup> Our model further supports the centralization of care for Moyamoya revascularization from a cost-effectiveness perspective to reduce procedural costs and maintain improved likelihood of excellent clinical outcomes.

Our model has several limitations. The first limitation pertains to generalizability, as our model assumes that patients with MMD are assumed to have a similar risk of subsequent stroke or perioperative morbidity. Similarly, our decision model captures the management decision for a patient presenting with hemorrhagic stroke utilizing the only prospective randomized data published to date. Further complexity can predict which patients are more likely to have increased post-operative morbidity such as variations in intraoperative blood pressure,<sup>15)</sup> increased age, and posterior cerebral artery stenosis<sup>33)</sup> as potential risk factors for perioperative stroke. To account for this additional nuance and model this increased complexity of inputs, the one-way, two-way, and probabilistic sensitivity analysis capture how our results would change across a range of values of perioperative morbidity and stroke rates associated with both operative and nonoperative management. We describe only direct revascularization as a surgical management option, as there was insufficient prospective randomized data regarding the impact of indirect revascularization on hemorrhagic stroke. However, existing retrospective data suggest that indirect and direct revascularization share similar costs and effectiveness,<sup>6)23)</sup> thus our model may also be applicable to indirect revascularization. Moreover, not all hem-

orrhagic strokes are associated with the same degree of disability. To mitigate this limitation, we model the degree of disability by utilizing the available data from intracerebral hemorrhage to capture the decline in neurologic functional status after cerebral hemorrhage. As further data on cost and health utility emerge, our future work can directly compare the cost-effectiveness of direct and indirect bypass for MMD.<sup>16)</sup> Costs were derived from existing published literature on surgical revascularization, admission for stroke, and neurologic disability, which may vary between different health care environments. This limitation was addressed through a one-way sensitivity analysis which demonstrated that when surgical costs remained less than \$85,000, substantially greater than the average surgical cost, surgical revascularization remained the dominant strategy.

Despite these limitations, our model is the first cost-effectiveness analysis to capture the impact of surgical revascularization on quality of life and health care costs for patients with MMD. This analysis can better inform patients, surgeons, and policy makers to understand how surgery for MMD can have a broad impact in improving quality of life for patients by preventing hemorrhagic stroke while also reducing rehabilitation costs associated with stroke related disability. Furthermore, surgery may reduce overall healthcare and societal costs. These findings should be used to further counsel patients and policymakers about the societal utility of neurosurgical intervention in the management of this disease.

## CONCLUSIONS

Considering both direct and indirect costs and post-operative QALY, surgical revascularization is more cost-effective than non-operative management for MMD in the United States. Surgery, which increases initial costs and risks, improves quality of life over both five-year and lifetime horizons and reduces total health care costs by preventing delayed stroke and neurologic disability.

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## Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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