Cost-Effectiveness of Transfers to Centers With Neurological Intensive Care Units After Intracerebral Hemorrhage

Jeffrey J. Fletcher, MD, MSc; Vikas Kotagal, MD, MSc; Aaron Mammoser, MD, MSc; Mark Peterson, PhD, MSc; Lewis B. Morgenstern, MD; James F. Burke, MD, MS

Background and Purpose—Our aim was to estimate the cost-effectiveness of transferring patients with intracerebral hemorrhage from centers without specialized neurological intensive care units (neo-ICUs) to centers with neo-ICUs.

Methods—Decision analytic models were developed for the lifetime horizons. Model inputs were derived from the best available data, informed by a variety of previous cost-effectiveness models of stroke. The effect of neo-ICU care on functional outcomes was modeled in 3 scenarios. A favorable outcomes scenario was modeled based on the best observational data and compared with moderately favorable and least-favorable outcomes scenarios. Health benefits were measured in quality-adjusted life years (QALYs), and costs were estimated from a societal perspective. Costs were combined with QALYs gained to generate incremental cost-effectiveness ratios. One-way sensitivity analysis and Monte Carlo simulations were performed to test robustness of the model assumptions.

Results—Transferring patients to centers with neo-ICUs yielded an incremental cost-effectiveness ratio for the lifetime horizon of $47,431 per QALY, $91,674 per QALY, and $380,358 per QALY for favorable, moderately favorable, and least-favorable scenarios, respectively. Models were robust at a willingness-to-pay threshold of $100,000 per QALY, with 95.5%, 75.0%, and 2.1% of simulations below the threshold for favorable, moderately favorable, and least-favorable scenarios, respectively.

Conclusions—Transferring patients with intracerebral hemorrhage to centers with specialized neo-ICUs is cost-effective if observational estimates of the neo-ICU–based functional outcome distribution are accurate. If future work confirms these functional outcome distributions, then a strong societal rationale exists to build systems of care designed to transfer intracerebral hemorrhage patients to specialized neo-ICUs. (Stroke. 2015;46:58-64. DOI: 10.1161/STROKEAHA.114.006653.)

Key Words: cerebral hemorrhage ■ cost-effectiveness ■ mortality

Specialized neurological intensive care units (neo-ICUs) with neurocritical care expertise are associated with lower mortality and improved functional outcome in spontaneous intracerebral hemorrhage (ICH).1–4 Given that randomized controlled trials have failed to identify interventions that improve outcome after ICH, and that a majority of patients with ICH are not treated in specialized centers,5,6 increasing use of hospital-based care in specialized neo-ICUs may represent an alternative opportunity to improve ICH outcomes.

Guidelines for the management of subarachnoid hemorrhage recommend that low-volume centers consider early transfer of patients to high-volume centers with experienced cerebrovascular surgeons, endovascular specialists, and a multidisciplinary neurocritical care service.7 This is based on literature demonstrating improved outcomes in centers that treat a higher number of patients with subarachnoid hemorrhage.8 Similarly, guidelines for the management of an acute ischemic stroke recommend treatment of not only patients with ischemic stroke in centers with verified stroke units9 but also patients with major hemispheric infarction be transferred to centers with neurosurgical expertise. On the contrary, guidelines for the management of a spontaneous ICH in adults recommend that management of patients takes place initially in an ICU; however, they do not recommend transferring patients to centers with specialized neo-ICUs or to high-volume centers.10

Our aim was to explore the cost-effectiveness of transferring patients with ICH from centers without neo-ICUs to centers with specialized neo-ICUs to inform stakeholders on ICH resource use.

Methods

Overview

We constructed a decision analytic model of a transfer strategy in which patients presenting to hospitals without neo-ICUs (−neo-ICUs) are transferred to hospitals with neo-ICUs (+neo-ICUs; compared with no transfer). +Neo-ICUs had to be led by an intensivist trained in neurocritical care. In the model, no transfer refers to the management at the presenting hospital in a medical or surgical ICU without neurocritical care expertise. We not only restricted our model to patients with severe ICH but also included the full spectrum of patients with ICH because it is difficult to predict who will...

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have early medical or neurological decline, and guidelines endorse all ICHs be initially admitted to an ICU. In addition, +neuro-ICU centers are more likely to have neurosurgery, vascular neurology, critical care electroencephalography, and the full spectrum of stroke unit capabilities, any and all of which may contribute to improved outcome after ICH.11,12 Given the lack of high-quality data on long-term outcomes in ICH, functional outcomes were assumed to be constant after 90 days. Hence, the analysis underestimates any functional outcome gains or declines achieved >90 days.

Model Structure
The model depicted in Figure 1, based on a cost-effectiveness model by Samsa et al,13 was implemented using TreeAge Pro 2013 software (TreeAge Software, Inc, Williamstown, MA). Deaths for the short-term horizon were assumed at 90 days and then assumed yearly with each cycle. Patients entered into the model by presenting to an emergency room with ICH at a −neuro-ICU center. Costs and outcomes were compared between those who were transferred to a +neuro-ICU center or those remaining at the −neuro-ICU center, based on 3 sets of parameters: population characteristics, functional outcomes, and costs. Outcomes from the model included direct costs (total cost being the sum of transfer, hospital costs, and caregiver costs) and quality-adjusted life years (QALYs). The model was populated with input parameters taken from peer-reviewed literature (Tables 1–3).13–22

### Population Characteristics
The age distribution of the population was 65 years (±10 years).14 Mortality rates for ICH survivors were stratified by modified Rankin Scale (mRS) score at 90 days. The mRS is a commonly used functional assessment scale after stroke. Age-specific all-cause mortality rates (US National Vital Statistics Report 2010) were risk-adjusted by death hazard ratios stratified by mRS score (Tables 1–3).13 The effectiveness outcome of interest (QALYs) was constructed by multiplying the utility weight associated with a certain mRS score by years of remaining life. A utility weight of 1.0 represents a state of perfect health and 0.0 represents death. QALYs were estimated by multiplying the number of life years within a particular health state by that health state’s utility weight. Ninety-day horizon QALY estimates were generated using 0.25 years of life. Utility weights associated with each mRS score were obtained from a previous study measuring quality of life after stroke.22 Sensitivity analysis was performed around these values because different studies have found slight differences in utility scores for certain mRS states.17 Cost-effectiveness was measured using the incremental cost-effectiveness ratio, which is calculated by dividing the difference in average costs per patient between transfer and no transfer by the difference in average QALYs.

### Functional Outcomes
Patients at −neuro-ICU centers were assigned a 90-day mortality risk of 32% based on the nationwide inpatient sample. The national inpatient sample represents ≈20% stratified sample of US community hospitals, the vast majority of which do not have Neurointensivist staffed neuro-ICUs.7 This risk estimate is consistent with other studies comparing mortality between −neuro-ICU and +neuro-ICU centers.12,19,20 Patients were assigned a 90-day mRS score based on expected distribution derived from a population-based study of ICH outcome.5,14 In this cohort, the mortality risk is similar to −neuro-ICU studies12,19,20 and the distribution of good functional outcome is similar to population-based studies in Europe.2,24 A reduction in 90-day mortality of 29% was associated with transfer and varied in sensitivity analysis based on the literature review.12,15,19,20

+Neuro-ICU centers have consistently been found to have lower mortality than −neuro-ICUs; however, less is known about differences in functional outcome in survivors as measured by functional outcome scales.13–22 Consequently, we modeled 3 different outcome scenarios (Figure 2; Tables 1–3). The best available observational data suggest a small and consistent improvement in functional outcomes among survivors at +neuro-ICUs.2,22 We based our favorable scenario on this data, in which the distribution of functional outcome in survivors at +neuro-ICU centers was proportionally redistributed among mRS scores (lowest obtainable mRS score 1). This assumes that +neuro-ICUs reduce mortality and improve functional outcome in survivors (not leaving more alive with severe disability). A second moderately favorable scenario was conceptually based on outcomes after decompressive hemicraniectomy for malignant hemispheric stroke, in which survivors because of mortality reduction after transfer had their functional outcomes redistributed among mRS scores 3 to 5.26 Finally, a least-favorable scenario assumed that all survivors from +neuro-ICUs survived in a severely disabled state (mRS=5).

### Costs
Costs were estimated for the 90-day horizon and annually for lifetime timeframes from a societal perspective. All costs were normalized to the year 2013.

### First 90-Day Costs
The cost of transfer was estimated from the literature as the mean cost of ground ambulance and helicopter transport then varied in sensitivity analysis.15,16 Patient care costs by mRS score were obtained from a large multicenter, multinational placebo-controlled randomized clinical trial aimed at treatment of ICH.21 Hospital costs, nursing home costs, other intermediate costs, rehabilitation, and home healthcare assistance costs were ascertained from a large multicenter, multinational placebo-controlled randomized clinical trial aimed at treatment of ICH.21 No cost was assumed for the infrastructure of neuro-ICUs because they already exist for subarachnoid hemorrhage and other patients with severe neurological injury.

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**Figure 1.** Cost-effectiveness model. A patient enters the model when he or she presents to an emergency room of a hospital without a dedicated neuro-intensive care unit. ICH indicates intracerebral hemorrhage; and mRS, modified Rankin Scale.
Table 1. Input Parameters for the Decision Analytic Models: Inputs Not Stratified by Modified Rankin Scale (Range)

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Transfer</th>
<th>No Transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td>14–16</td>
<td>65 (±10)</td>
<td>65 (±10)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transfer costs</th>
<th>$2379 ($1190–$4759)</th>
<th>0 (0)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Post 90-d annual medical costs</th>
<th>$6659 (±20%)</th>
<th>$6659 (±20%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>scenario, were used to estimate lifetime and scatter plots were developed to represent uncertainty. Analyses were run 10,000× to capture stability in the results for each rele...</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Input Parameters for the Decision Analytic Models: Functional Outcome at 90 Days

<table>
<thead>
<tr>
<th>Proportional Distribution in Survivors at 90 d, %</th>
<th>No Transfer, %</th>
<th>Transfer Favorable, %</th>
<th>Transfer Moderately Favorable, %</th>
<th>Transfer Least Favorable, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3</td>
<td>2</td>
<td>2.3</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>22</td>
<td>15</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>9</td>
<td>10.2</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>16</td>
<td>18.2</td>
<td>20</td>
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<td>4</td>
<td>32</td>
<td>22</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>4</td>
<td>4.6</td>
<td>4.9</td>
</tr>
<tr>
<td>6</td>
<td>...</td>
<td>32</td>
<td>22.7</td>
<td>22.7</td>
</tr>
</tbody>
</table>

mRS indicates modified Rankin Scale.

Table 3. Input Parameters for the Decision Analytic Models: Inputs by mRS Score

<table>
<thead>
<tr>
<th>mRS Score</th>
<th>Costs in First 90 d (Range)</th>
<th>Cost Multipliers (Range)</th>
<th>Utility (Range)</th>
<th>Death Hazard (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>$9466 ($7130–$11 802)</td>
<td>1 (1–1)</td>
<td>0.85 (0.8–1)</td>
<td>1 (1–0.5)</td>
</tr>
<tr>
<td>1</td>
<td>$15 547 ($13 336–$17 757)</td>
<td>1 (1–1)</td>
<td>0.80 (0.75–0.9)</td>
<td>1 (1–0.5)</td>
</tr>
<tr>
<td>2</td>
<td>$18 742 ($15 987–$21 496)</td>
<td>1.27 (1.04–1.7)</td>
<td>0.70 (0.53–0.75)</td>
<td>1.11 (1–0.5)</td>
</tr>
<tr>
<td>3</td>
<td>$27 387 ($24 372–$30 402)</td>
<td>1.94 (1.3–2.5)</td>
<td>0.51 (0.45–0.65)</td>
<td>1.27 (1.2–1.4)</td>
</tr>
<tr>
<td>4</td>
<td>$27 281 ($25 198–$29 364)</td>
<td>3.98 (1.7–7)</td>
<td>0.30 (0.25–0.55)</td>
<td>1.71 (1.3–2.0)</td>
</tr>
<tr>
<td>5</td>
<td>$27 330 ($22 182–$32 479)</td>
<td>6.01 (2.05–10)</td>
<td>0.15 (0–0.32)</td>
<td>2.37 (1.5–4.0)</td>
</tr>
<tr>
<td>6</td>
<td>$8136 ($7241–$9032)</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
</tr>
</tbody>
</table>

mRS indicates modified Rankin Scale.

Long-Term Costs

Similar to other recent cost-effectiveness analyses for stroke, estimates of cost after 90 days were based on annual costs obtained from Medicare data. Long-term stroke-specific cost multipliers, based on 90-day mRS scores, were used to estimate lifetime costs based on life expectancy. Long-term care costs included annual medical costs (inpatient and outpatient), caregiver costs and other long-term expenses.

Sensitivity Analysis

For each scenario, sensitivity analyses were performed to test the robustness of specific model assumptions/parameters. First, we examined changing multiple individual parameters in 1-way sensitivity analysis across plausible ranges (Tables 1–3). Parameters analyzed included age, cost multipliers, death hazard ratios, utility weights, cost of transfer, and discount rate.

We also performed a probabilistic sensitivity analysis (second-order Monte Carlo simulation) in which all parameters in 1-way sensitivity analysis were varied simultaneously. Variable ranges distributions around the parameter point estimate were taken from the literature. The distribution field was normal for discount rate and short-term costs. mRS indicates modified Rankin Scale.

Results

Base-Case

In each scenario, transfer to a neuro-ICU center resulted in an increase in QALYs although this effect was modest in the least-favorable scenario. The incremental cost-effectiveness ratio for the lifetime horizon of transferring patients to +neuro-ICU centers (compared with no transfer) is $47 431 per QALY, $91 674 per QALY, and $380 358 per QALY for the favorable, moderately favorable, and least-favorable scenarios, respectively. Hence, using the cost-effectiveness threshold of $100 000 per QALY for both the favorable and moderately favorable scenarios was cost-effective but the least-favorable scenario was not (Table 4).

One-Way Sensitivity Analysis for the Lifetime Horizon

The models were robust for death hazard ratios, base age, transfer cost, and for utility weights and cost multipliers for patients with less disability (mRS≤4). All models were expectedly sensitive to the reduction in mortality. The favorable and moderately favorable scenarios were also sensitive to the cost multipliers for patients with mRS score of 4 and were relatively sensitive to discount rate. In addition to mortality reduction, the least-favorable scenario was also sensitive to the utility score for patients with mRS score of 5. Varying other inputs would not make this scenario cost-effective (Figure 3).

Multiway Probabilistic Sensitivity Analysis

Figure 4 presents the joint distribution of cost and effectiveness differences in the cost-effectiveness plane for each of the 3 scenarios in which all parameters were varied simultaneously >10000 iterations. In the favorable and moderately favorable scenarios, transfer seemed cost-effective, with the majority of simulations below the willing-to-pay (WTP) threshold of...
$100,000 per QALY (95.5% favorable scenario; 75.0% moderately favorable scenario). For the least-favorable scenario, the majority of simulations (97.9%) were above the $100,000 per QALY WTP threshold. Because some have argued that the cost-effectiveness threshold should be $50,000 per QALY, we also performed the analysis at a WTP threshold of $50,000 per QALY (Figure 4). In this scenario, the majority of simulations were above the WTP threshold except in the favorable scenario, in which 58.1% of simulations were still below the threshold.

### Discussion

Under the assumptions of the model, transferring patients with ICH to specialized neuro-ICUs is likely cost-effective, even if specialized neuro-ICUs only have a moderately positive effect on functional outcomes. Given the paucity of high-quality data on the effect of neuro-ICUs on functional outcomes, this analysis explored a variety of assumptions on functional outcomes and found specialized neuro-ICU care is associated with an acceptable cost per QALY if mortality reduction is not solely because of leaving more patients alive with severe disability. In the favorable and moderately favorable scenarios, this cost was $47,000 per QALY and $91,000 per QALY, respectively. Assuming a WTP threshold of $100,000 per QALY, the findings of the base-case analysis seem robust among the favorable and moderately favorable scenarios and are supported by sensitivity analyses. However, if the WTP threshold is lowered to $50,000 per QALY, transferring patients to centers with neuro-ICUs may only be cost-effective in the favorable scenario.

Although our findings highlight that the cost-effectiveness of transferring ICH patients to centers with neuro-ICUs depends heavily on the distribution of functional outcome in survivors, whether a specific cost-effectiveness threshold should be used in medical care is debated. Currently, there is a wide range of lifetime horizon incremental cost-effectiveness ratios for commonly performed procedures in acute neurology. For example, tissue-type plasminogen activator for acute ischemic stroke in the 0- to 3-hour window is cost-saving, whereas the cost-effectiveness for decompressive craniectomy after severe traumatic brain injury is reported to be >$670,000 per QALY. For comparison, our findings for the lifetime horizon in the favorable and moderately favorable scenarios were between the cost-effectiveness of tissue-type plasminogen activator therapy for acute ischemic stroke within 3 to 4.5 hours from stroke onset ($22,000 per QALY) and for decompressive craniectomy after severe ischemic stroke ($82,000 per QALY).

Our finding that transferring patients after ICH to centers with neuro-ICUs is likely cost-effective and has public health and policy implications. Interactions within stroke systems of care aim to improve survival and functional outcome after stroke by promoting administration of intravenous tissue-type plasminogen activator and the development of telemedicine services and stroke units. These measures improve functional outcome, resulting in cost-effective care. Hence, the American Stroke Association recommends that the vast majority of patients with acute stroke should be cared for at a primary or comprehensive stroke center regardless of where they enter the healthcare system. In addition, these recommendations support neurocritical care beds and expertise at comprehensive stroke centers; however, they do not specify that care happens in a neuro-ICU or is led by a neurocritical care-trained intensivist. If neuro-ICUs improve survival and functional outcome with an acceptable cost per QALY, then the development of specialized neuro-ICUs should be encouraged at comprehensive stroke centers, as well as routing of patients with ICH to these centers regardless of where they enter the healthcare system.

Expectedly, all 3 models were sensitive to a reduction in mortality, as well as cost multipliers and utility scores. In addition, higher levels of disability were associated with increased incremental cost-effectiveness ratio ranges. However, unless these estimates were at or beyond the extremes of the modeled parameter distributions, changing these inputs would not likely change cost-effectiveness considerations, given the results of the multiway sensitivity analysis.

Our study has limitations. First, we postulated the benefit of transfer would apply to all patients, even though some ICHs are small and survivable with mild disability. However, no data suggest that small hemorrhages would not benefit from transfer, analogous to the effect of stroke units on outcomes after transient ischemic attack and ischemic stroke. Second, we estimated distributions of functional outcomes because comparisons between centers with and without neuro-ICUs in the literature are limited. Third, the functional outcomes were conservatively assumed to be stable at 90 days. Wider use of constraint that induced movement therapy or other care advancements could improve functional outcomes, increase the gain in QALYs, and possibly reduce net lifetime costs. Fourth, we also used separate estimates from previously published literature for our input parameters, which prevents us from considering potential covariation among the costs and functional outcomes. However, inputs, including costs, were from high-quality studies of ICH and stroke and varied over reasonable ranges in 1-way and multiway sensitivity analysis. Finally, we assumed that current neuro-ICUs could absorb the volume of patients transferred which is unclear although changing with the development of comprehensive stroke centers.
Figure 3. Tornado diagrams depicting the results of 1-way sensitivity analysis for favorable (A), moderately favorable (B), and least-favorable scenarios (C). Horizontal bars represent incremental cost-effectiveness ratio associated with upper and lower bounds for that particular input parameter. mRS indicates modified Rankin Scale.
Conclusions
Transferring patients to neuro-ICUs after ICH is cost-effective if observational study estimates of favorable shifts in the distribution of functional outcomes related to neonatal ICU care are accurate. Additional research should focus on differences in the distribution of functional outcomes between neuro-ICUs and other models of care. If such effects are confirmed to exist, there would be a strong societal rationale for stroke
systems of care to support development of neuro-ICU models and encourage transferring patients with ICH to these centers.

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None.

References
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