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Abstract

Background: American Stroke Association guidelines for prehospital acute ischemic stroke recommend against bypassing an intravenous tPA-ready hospital (IRH), if additional transportation time to an endovascular-ready hospital (ERH) exceeds 15–20 min. However, it is unknown when the benefit of potential endovascular therapy at an ERH outweighs the harm from delaying intravenous therapy at a closer IRH, especially since large vessel occlusion (LVO) status is initially unknown. We hypothesized that current time recommendations for IRH bypass are too short to achieve optimal outcomes for certain patient populations. **Methods**: A decision analysis model was constructed using population-based databases, a detailed literature review, and interventional trial data containing time-dependent modified Rankin Scale distributions. The base case was triaged by Emergency Medical Services (EMS) 110 min after stroke onset and had a 23.6% LVO rate. Base case triage choices were (1) transport to the closest IRH (12 min), (2) transport to the ERH (60 min) bypassing the IRH, or (3) apply the Cincinnati Stroke Triage Assessment Tool and transport to the ERH if positive for LVO. Outcomes were assessed using quality-adjusted life years (QALYs). Sensitivity analyses were performed for all major variables, and alternative prehospital stroke scales were assessed. **Results**: In the base case, transport to the IRH was the optimal choice with an expected outcome of 8.47 QALYs. Sensitivity analyses demonstrated that transport to the ERH was superior until bypass time exceeded 44 additional minutes, or when the onset to EMS triage interval exceeded 99 min. As the probability of LVO increased, ERH transport was optimal at longer onset to EMS triage intervals. The optimal triage strategy was highly dependent on specific interactions between the IRH transportation time, ERH transportation time, and onset to EMS triage interval. **Conclusions**: No single time difference between IRH and ERH transportation optimizes triage for all patients. Allowable IRH bypass time should be increased and acute ischemic stroke guidelines should incorporate the onset to EMS triage interval, IRH transportation time, and ERH transportation time.

Key Words emergency medical services; triage; ischemic stroke; decision support techniques; endovascular procedures; tissue plasminogen activator

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Address correspondence to Justin L. Benoit, MD, MS, 231 Albert Sabin Way, P.O. Box 670769, Cincinnati, OH 45267-0769, USA. E-mail: justin.benoit@uc.edu

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Introduction

The public health burden of acute ischemic stroke is tremendous, with an annual incidence of ~700,000 in the United States (1). Recent trials of reperfusion treatment for acute ischemic stroke have demonstrated improved patient outcomes with endovascular therapy (EVT) compared to treatment with intravenous recombinant tissue-type plasminogen activator (IVT) (2). As such, EVT has become an important component of stroke care. However, system-wide implementation is challenging. EVT is only available at the highest level of inpatient stroke facilities, typically those certified as comprehensive stroke centers, and only ~100 presently exist in the United States (3). As a result, some patients may be 120 min from the nearest endovascular-ready hospital (ERH) (4). Intravenous tPA-ready hospitals

(IRH), typically primary stroke centers and acute stroke-ready hospitals, are more numerous but generally do not have endovascular capabilities.

Emergency Medical Services (EMS) has a pivotal role in stroke care, as up to 64% of acute strokes are transported to the hospital by EMS (5,6). Given that time to treatment is critical for both EVT and IVT, the importance of hospital destination choice by EMS may increase with wider implementation EVT (7–10). However, it is unknown when the benefit of possible EVT at an ERH outweighs the potential harm from bypassing IVT at an IRH. This harm is particularly evident in patients ineligible for EVT due to the absence of large vessel occlusion (LVO). Alternatively, patients with LVO may be harmed if transported initially to an IRH, due to subsequent delays associated with secondary transfer for EVT at an ERH. A policy statement from the American Stroke Association suggests that EMS should not bypass an IRH in favor of an ERH if diversion would add more than 15–20 min to the transportation time (3,11). Prehospital stroke triage tools have been developed to identify patients with severe strokes who may gain the most benefit from immediate transport to an ERH due to an underlying LVO, but definitive prospective validation in prehospital stroke populations is lacking (12–15).

To provide better guidance to EMS providers, we sought to evaluate different prehospital transportation triage strategies for acute ischemic stroke and determine which variables affect patient outcomes. Specifically, we addressed the following question: When should EMS bypass immediate IVT at an IRH and instead go to an ERH for possible EVT, and can prehospital triage tools improve that decision? Our hypothesis was that current time recommendations for IRH bypass are too short to achieve optimal outcomes for certain patient populations. We chose a decision analytic approach because of its ability to systematically and quantitatively incorporate multiple sources of data and provide clinically relevant answers.

METHODS

Overview

Decision analysis involves: (1) gathering relevant clinical data, (2) fitting these data onto a framework representing standard clinical care, (3) defining an average patient (called the "base case") to simulate a clinical encounter, and (4) analyzing alternative scenarios to develop generalizable conclusions that inform clinical practice. For readers unfamiliar with decision analysis, we suggest the following series of articles (16–20).

In the following sections, we describe: (1) the data entered into the model, (2) the structure of the model itself, and (3) the technique for model analysis. Base case values were chosen using population-based sources, including individual patient-level data and previously published summaries from the literature. We explored uncertainty surrounding these values and their effect on the model using sensitivity analyses. Base case values and ranges tested are explained in the following sections and listed in Table 1. This study was deemed exempt by our Institutional Review Board.

Review of Data Used for Modeling

Transportation and Treatment Times

The population-based Greater Cincinnati/Northern Kentucky Stroke Study's dataset was used for the base case time from stroke onset or last seen normal time to Emergency Department arrival for confirmed ischemic stroke patients transported from the scene by EMS (21). A median value of 122 min was observed. The average transportation time to the initial hospital (generally an IRH) was 12 min in this region, making the interval between stroke onset and EMS triage decision 110 min. Epidemiological studies of the United States population suggest that most acute strokes occur within a 60-min transportation window to an ERH (56% by ground, 85% by air), so this was used for ERH transportation time (4,22). Studies of aeromedical transport of acute ST-segment elevation myocardial infarction was used to model the significant time delay (41 min) inherent in transferring a patient with a time-dependent disease from a lower-level facility to a higher-level facility (23,24). This includes the time between transportation request and helicopter lift, flight time to pick up the patient, and time spent by the crew at the initial hospital.

Published data detailing endovascular workflow times that include hospital arrival to IVT treatment (door-to-needle) time are limited. As such, the model used a median time of 45 min, based on the only endovascular trial reporting this interval (25). This time coincides with optimal treatment goals from the American Stroke Association (26). Pooled endovascular trial data demonstrated the median time from treatment decision to groin puncture was 69 min, and 44 min from puncture to reperfusion or procedure completion (2,27). The model required initiation of EVT (groin puncture) within 6 h of stroke onset and IVT within 4.5 h, as currently recommended by clinical guidelines (10,11,28).

Probability of LVO

SITS-ISTR is a multinational, open registry of consecutive acute ischemic stroke patients who received reperfusion therapies at 132 centers. SITS-ISTR observed a LVO rate of 23.6%, with a National Institutes of Health Stroke Scale (NIHSS) score of 6–10 most common

TABLE 1. Variables in the decision analysis model

Parameter	Value for Base Case *(Range Tested in Sensitivity Analyses)*
Time (min)	
Stroke onset to EMS triage interval (21)	110 *(0–220)*
Transportation time to IRH (21)	12 *(36, 60)*
Transportation time to ERH (4,22)	60 *(0–150)*
IRH to ERH transfer delay (23,24)	41
Initial hospital evaluation (door to needle) (25,26)	45
Treatment decision to groin puncture (2,27)	69
Groin puncture to reperfusion (2,27)	44
Onset to IVT maximum (28)	270
Onset to groin puncture maximum (EVT) (10,11)	360
Probability of LVO (5,6,29,30)	0.236 *(0.087, 0.364)*
Probability of no exclusions to EVT (25)	0.783
Probability of reperfusion (2)	0.71
Annual mortality rate (43,44)	0.065

Diagnostic tests	**Sensitivity**	**Specificity**
C-STAT (12)	83	40
LAMS (14)	*(81)*	*(89)*
RACE (13)	*(85)*	*(67)*
3I-SS (15)	*(67)*	*(92)*
95% (45)	*(95)*	*(95)*

Probability of stroke outcomes	**mRS 0**	**mRS 1**	**mRS 2**	**mRS 3**	**mRS 4**	**mRS 5**	**mRS 6**
No LVO with no reperfusion treatment (35)	0.2424	0.2727	0.1717	0.1111	0.0909	0.0202	0.0909
LVO with no reperfusion treatment (35)	0.0423	0.108	0.0939	0.1596	0.2488	0.0892	0.2582
No LVO with IVT (36)							
45.5 min (onset to needle)	0.4317	0.2228	0.1045	0.1053	0.0518	0.0108	0.0731
135.5 min	0.2410	0.4138	0.1108	0.0791	0.0482	0.0136	0.0936
225.5 min	0.3334	0.2510	0.1625	0.0761	0.0610	0.0220	0.0941
LVO with IVT (36)							
45.5 min (onset to needle)	0.0979	0.1147	0.0743	0.1966	0.1844	0.0622	0.2699
135.5 min	0.0502	0.1957	0.0723	0.1356	0.1574	0.0715	0.3173
225.5 min	0.0656	0.1121	0.1002	0.1232	0.1883	0.1093	0.3014
LVO with successful EVT (39)							
158.5 min (onset to reperfusion) (2,27)	0.9641	0.0056	0.0022	0.0097	0.0076	0.0051	0.0058
	(0.161)	*(0.265)*	*(0.243)*	*(0.161)*	*(0.088)*	*(0.035)*	*(0.048)*
248.5 min	0.1232	0.4400	0.0435	0.1109	0.1609	0.0088	0.1128
338.5 min	0.1047	0.2148	0.0565	0.0984	0.2256	0.1745	0.1255
LVO with unsuccessful EVT (39)							
158.5 min (onset to procedure end)	0.0772	0.0969	0.0329	0.2491	0.2388	0.0350	0.2702
248.5 min	0.0408	0.1703	0.0330	0.1770	0.2101	0.0415	0.3274
338.5 min	0.0542	0.0992	0.0465	0.1637	0.2556	0.0645	0.3163
Death Hazard (41,42)	1	1	1.11	1.27	1.71	2.37	
Utilities (41,42)	0.8	0.8	0.65	0.5	0.35	0.2	0

EMS = *Emergency Medical Services*; IRH = *Intravenous tPA-ready hospital*; ERH = *Endovascular-ready hospital*; IVT = *Intravenous recombinant tissue-type plasminogen activator*; EVT = *Endovascular therapy*; LVO = *Large vessel occlusion*; C-STAT = *Cincinnati Stroke Triage Assessment Tool*; LAMS = *Los Angeles Motor Scale*; RACE = *Rapid Arterial Occlusion Evaluation scale*; 3I-SS = *3-Item Stroke Scale*; 95% = *Hypothetical near-perfect test*; mRS = *Modified Rankin Scale*.

(29,30). Acute ischemic stroke patients transported by EMS have a similar median NIHSS score at 8, which is higher than the overall stroke population (5,6). LVO was defined as occlusion of the internal carotid artery or the main stem of the middle cerebral artery (M1), consistent with current endovascular guidelines.

Prehospital Stroke Scales

Several prehospital scoring systems based on physical exam findings have been proposed to identify patients likely to have severe strokes and/or LVO, including the Cincinnati Stroke Triage Assessment Tool (C-STAT), the Los Angeles Motor Scale (LAMS), the Rapid Arterial Occlusion Evaluation Scale (RACE), and the 3-Item Stroke Scale (3I-SS) (12-15). The C-STAT was used for the base case due to theoretical ease of implementation, strong correlation with LVO and NIHSS, and ongoing independent prospective validation in the prehospital setting (12,31,32). The retrospective validation cohort demonstrated a sensitivity and specificity of 83% and 40% for LVO with a score ≥2. Alternative prehospital stroke scales are described in the following sections.

Endovascular Therapy

The likelihood of achieving angiographic reperfusion after EVT was set at 71% based on recent endovascular trials (2). Reperfusion is assessed using the modified Thrombolysis in Cerebral Infarction score (33).

Successful reperfusion was defined as a score of 2b or 3, while unsuccessful reperfusion was a 0, 1, or 2a. We modeled some patients with LVO as ineligible for EVT using rates reported in the EXTEND-IA trial: 4% for large ischemic core, 16% for poor premorbid condition, and 1.7% for poor vascular access (25).

Time-Dependent Clinical Outcomes

Patient outcomes were modeled using 90-d post-stroke disability, measured using the modified Rankin Scale (mRS) (34). Importantly, stroke outcomes are dependent on treatment times for both IVT and EVT (7–10). Calculations of outcomes are described in the following sections.

Description of Decision Analytic Model

Decision Tree

The decision tree examines 3 triage strategies for EMS: (1) transport to the closest IRH, (2) bypass the IRH and transport to the ERH directly, or (3) apply the C-STAT and transport to the ERH if positive or the IRH if negative (Figure 1). Transportation, evaluation, and treatment times are additive as a hypothetical patient moves through the decision tree (Table 1). In the IRH arm, patients with LVO receive IVT prior to transfer to the ERH ("drip-and-ship"), but incur delays to EVT due to additional ERH transportation time and inherent delays in transfer. In the C-STAT arm, Bayes' theorem is used to determine the post-test probability of LVO (based on the sensitivity and specificity of the C-STAT and the pre-test probability of LVO) and then applied to rest of the model. Each branch ends with a mRS outcome distribution. These distributions are used to calculate the expected number of quality-adjusted life years (QALYs) an individual patient would be expected to achieve post-stroke, as described in the following sections. The triage strategy yielding the largest number QALYs is the optimal strategy to pursue.

Clinical Outcomes

Six different mRS outcome distributions were calculated as a function of time from stroke onset to treatment: (1) no LVO with no reperfusion treatment, (2) LVO with no reperfusion treatment, (3) no LVO with IVT, (4) LVO with IVT, (5) LVO with successful EVT, and (6) LVO with unsuccessful EVT. For modeling purposes, time was measured in 90-min blocks, linear interpolation was used to calculate per minute values between blocks, and outcomes were set equal at treatment window termini. Outcome data were derived from clinical trials, so NIHSS distributions relevant to outcomes for moderate and severe strokes were already captured by the mRS distributions.

Data from the placebo arm of the NINDS trials demonstrating IVT benefit were used to estimate mRS distributions for patients who receive no reperfusion treatment (35). The stroke severity of the NINDS cohort was higher than the overall stroke population, but EMS transported strokes are also more severe than the overall stroke population (5,6). LVO status was not assessed directly in trials with placebo arms, and these data are unlikely to become available due to lack of clinical equipoise (36). Therefore, receiver operating characteristic curves were used to predict LVO status based on NIHSS, with an inflection point at a NIHSS score of 10 (37-39). Thus, presence or absence of LVO was defined by a NIHSS score of >10 and ≤ 10 to calculate outcomes after no reperfusion treatment (Table 1). Reassuringly, these calculated outcomes coincided with a theoretically similar cohort, in which 24.4% of patients with failed LVO recanalization on post-IVT imaging studies had good outcomes (mRS of 0–2) (40).

Published pooled data from available randomized trials of placebo versus IVT were used to calculate time-dependent mRS-specific relative risks (36). These relative risks were then multiplied by the no reperfusion treatment mRS distributions to calculate IVT outcomes stratified by LVO status (Table 1). The use of relative risks instead of absolute outcomes allowed the model to be agnostic to random differences and secular trends in stroke care. Therefore, the absolute outcomes from the NINDS cohort are simply the floor upon which the model is built, and raising or lowering this floor would not affect the relative outcomes of different triage strategies. Adequate data do not exist to stratify IVT outcomes by recanalization status. However, this is irrelevant for the model as both outcomes are captured by existing trial data, and there is no evidence that rates of recanalization after IVT have changed over time.

Endovascular outcomes were calculated using IMS III trial data (39). Alternative endovascular trial data were not publicly available nor provided upon request, and published summaries were inadequate (2,27). However, the time-dependent outcomes for EVT in IMS III have been similar to more recent endovascular trials (9,10). Furthermore, the success of recent endovascular trials compared to earlier attempts is thought to be due to quicker reperfusion times, better imaging techniques to identify patients with LVO and potentially salvageable brain tissue, and improved endovascular devices (9,39,41). These variables were easily corrected for in the model by using time-dependent outcomes, limiting data to only patients with LVO confirmed on CT angiography, and adjusting the probability of successful reperfusion to be consistent with contemporary devices. As such, the negative trial status of the original study is irrelevant for modeling purposes. Although IMS III used a slightly different definition of LVO by including occlusion of the branch of the middle cerebral artery (M2), few of these were

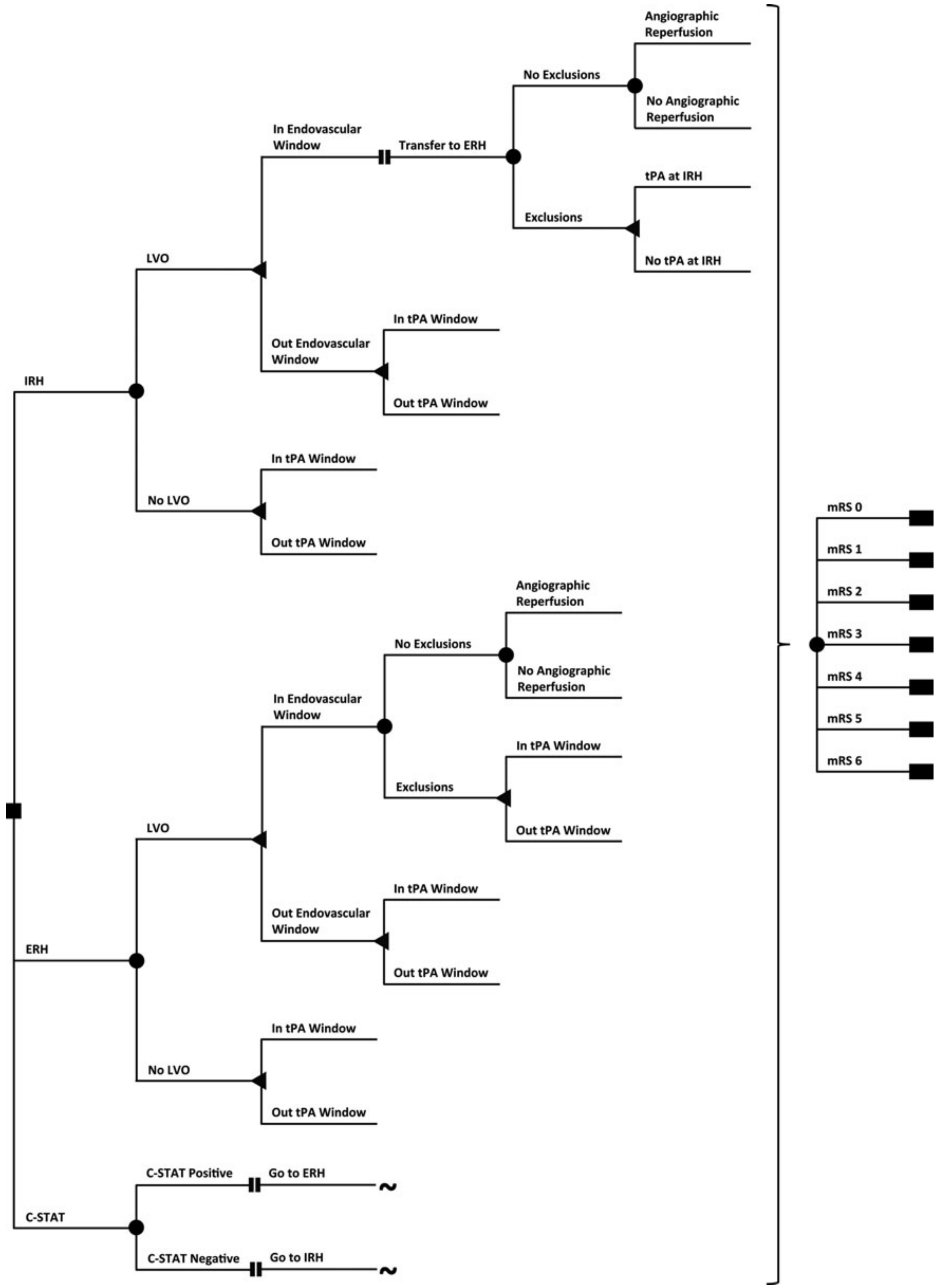


Figure 1. Decision tree.

The square represents the decision node with 3 triage strategies: (1) transport to the intravenous tPA-ready hospital (IRH), (2) transport to the endovascular-ready hospital (ERH), or (3) apply the Cincinnati Stroke Triage Assessment Tool (C-STAT) and transport to the ERH if positive or IRH if negative. Circles are chance nodes that model the likelihood of large vessel occlusion (LVO), exclusion to endovascular therapy, angiographic reperfusion after endovascular therapy, Bayes' theorem, and modified Rankin Scale (mRS) distributions. Double bars are label nodes that describe specific events in the model. Triangles are Boolean nodes that model treatment time windows for endovascular therapy and intravenous tissue plasminogen activator (tPA). Rectangles are terminal nodes that model the utility of outcomes.

actually enrolled in the study. Time-dependent mRS-specific relative risks for IVT versus EVT were calculated for both successful and unsuccessful EVT. These relative risks were multiplied by the previously calculated outcomes for IVT to calculate EVT outcomes (Table 1).

Quality of Life

Effectiveness was measured in QALYs, which accounts for both the length and quality of life, and is the standard method for quantifying outcomes in decision analysis. Each mRS score was considered a separate health state, and patient-assigned utility scores have been validated previously (Table 1) (41,42). These utility scores take into account patient preferences for varying levels of disability after stroke. A life expectancy of 15.5 years was used based on life table data from the National Center for Health Statistics for a 69-year-old patient (43). The declining exponential approximation of life expectancy method was used to determine the average annual mortality rate of 0.065 (44). Life expectancy was further adjusted by accounting for mRS-specific excess mortality risk (Table 1) (41,42). QALYs were calculated by multiplying the appropriate mRS-dependent life expectancy by the mRS-dependent utility score.

Model Assumptions

Simplifying assumptions of the decision analytic model are: (1) ERH transportation time is unchanged if initially transported to the IRH, (2) initial hospital assessment of LVO status is 100% accurate, (3) EVT outcomes are independent of IVT administration, and (4) patients remain in a constant state of health after the 90-d mRS evaluation.

Analysis

Decision Maker (Boston, MA) was used to construct the decision analytic model, analyze results, and perform sensitivity analyses. One-way sensitivity analyses (allowing a single variable to vary continuously) were conducted on the transportation time to ERH and the onset to EMS triage interval. Two-way sensitivity analyses (allowing 2 variables to vary simultaneously) were conducted on the onset to EMS triage interval versus both ERH and IRH transportation times. Alternative prehospital stroke scales were evaluated, including a hypothetical test with sensitivity/specificity similar to CT angiography at 95% (Table 1) (12–15,45). Further sensitivity analyses evaluated LVO probabilities of 8.7% and 36.4%. These were calculated using data from the SITS-ISTR cohort to correlate to the 25th and 75th percentile NIHSS score in the American Stroke Association's national registry of acute ischemic stroke patients transported by EMS (5,29,30). The outcome distribution for the earliest successful EVT time was based on small patient numbers; therefore, a final sensitivity analysis replaced this mRS distribution with a similar cohort from pooled endovascular data (Table 1) (2,27).

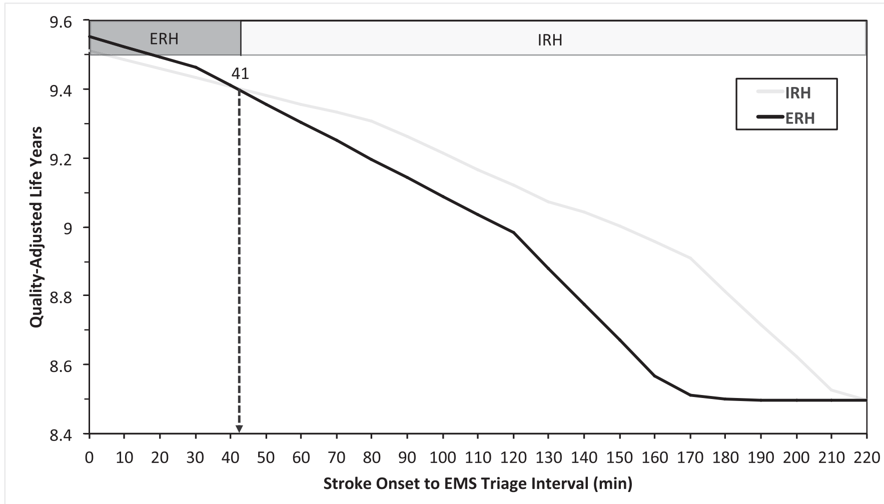
RESULTS

We first compared only the ERH and IRH triage strategies, excluding the C-STAT arm. In the base case (12 min to IRH; 60 min to ERH), transport to the IRH is the optimal choice with an expected outcome of 8.47 QALYs. A one-way sensitivity analysis of the ERH transportation time demonstrates that transport directly to the ERH is superior if the ERH is <56 min away, which is 44 additional minutes of transport due to IRH bypass.

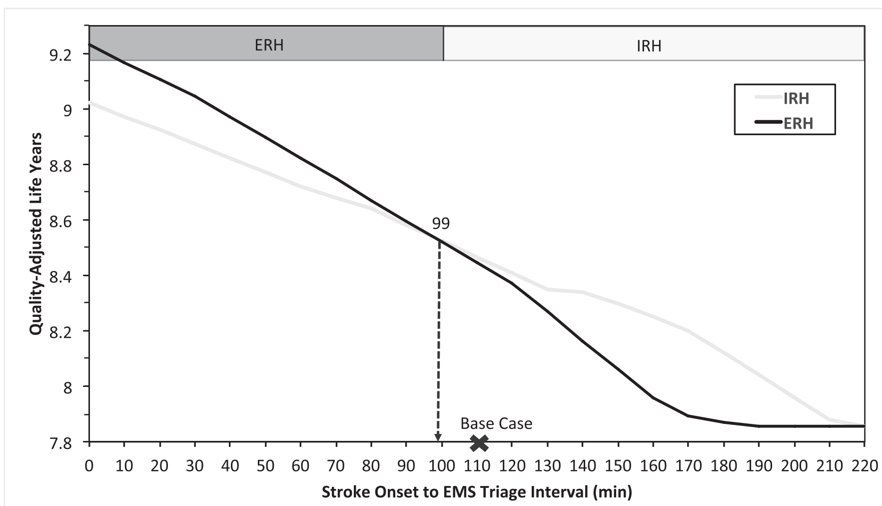
Figure 2 examines one-way sensitivity analyses of the stroke onset to EMS triage interval for 3 different probabilities of LVO, again excluding the C-STAT arm. Using the base case probability of LVO (23.6%), ERH transport is favored when the onset to EMS triage interval is <99 min, while IRH transport is favored at longer time intervals (Figure 2B). When the probability of LVO is smaller (8.7%), transport to the ERH is optimal only when the time interval is very short (Figure 2A). When the probability of LVO is larger (36.4%), transport to the ERH is optimal over a greater range of times (Figure 2C).

Figure 3 examines prehospital strokes scales for LVO, including the C-STAT, while still allowing the onset to EMS triage interval to vary. Only the thresholds between strategies are shown. Prehospital strokes scales are optimal at intermediate time intervals. When the probability of LVO is smaller (8.7%), transport to the ERH is never optimal, except through the use of a prehospital stroke scale. Improvements in the sensitivity or specificity increase the overall utility of the testing strategy. Increased sensitivity decreases the relative utility of the ERH strategy, while increased specificity decreases the relative utility of the IRH strategy. However, even the hypothetical near-perfect test, equivalent to CT angiography, still has a threshold after which IRH transport is optimal, regardless of the probability of LVO.

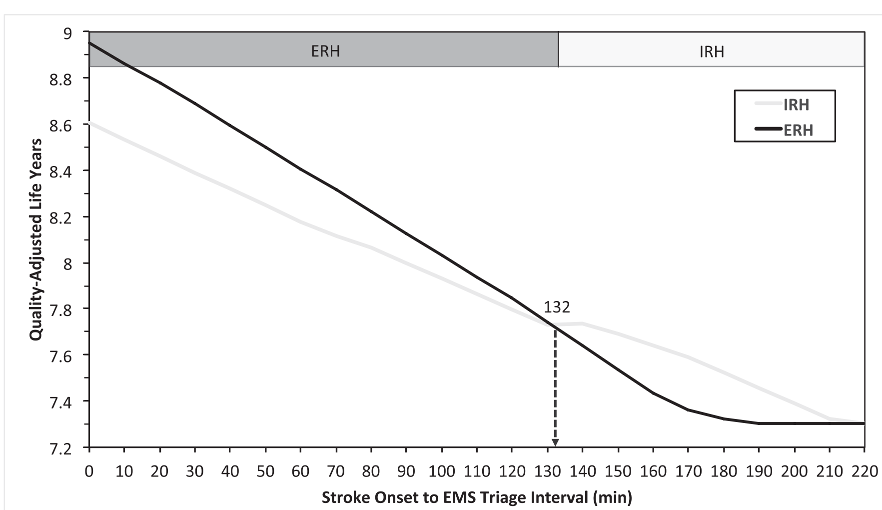
Figure 4 examines two-way sensitivity analyses for the onset to EMS triage interval (x-axis), and ERH transportation time (y-axis), further stratified by 3 different IRH transportation times and 2 different probabilities of LVO. In general, the IRH strategy is favored when onset to EMS triage intervals and ERH transportation times are long, the ERH strategy is favored when both time parameters are short, and the C-STAT is favored at intermediate times. Increases in IRH transportation time decrease the utility of the IRH strategy, while decreases in the probability of LVO decrease the utility of the ERH strategy. Importantly, the optimal



(A)



(B)



(C)

Figure 2. One-way sensitivity analyses of stroke onset to emergency medical services (EMS) triage interval. Three probabilities of large vessel occlusion (LVO) were evaluated. Lines represent 2 triage strategies: (1) transport to the intravenous tPA-ready hospital (IRH), or (2) transport to the endovascular-ready hospital (ERH). Shaded bars represent when a triage strategy is optimal. Dashed lines indicate thresholds.

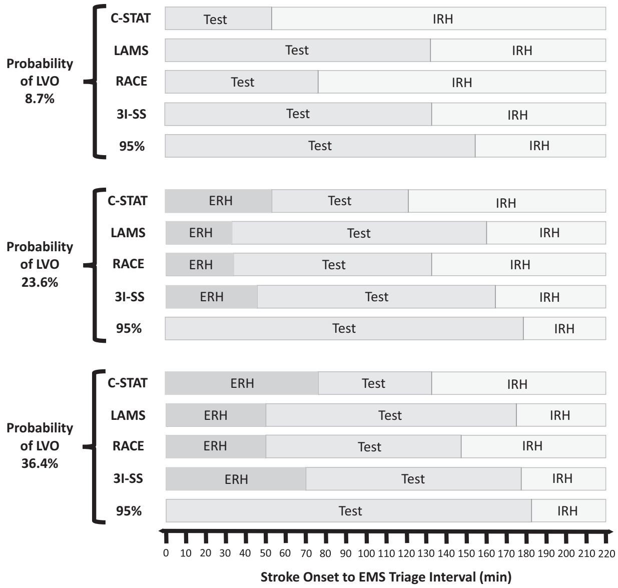


FIGURE 3. Thresholds for stroke onset to emergency medical services (EMS) triage interval using prehospital stroke scales for large vessel occlusion (LVO). Three probabilities of LVO were evaluated. Shaded bars represent when each triage strategy is optimal: (1) transport to the intravenous tPA-ready hospital (IRH), (2) transport to the endovascular-ready hospital (ERH), or (3) apply the prehospital stroke scale (Test) and transport to the ERH if positive. C-STAT: Cincinnati Stroke Triage Assessment Tool; LAMS: Los Angeles Motor Scale; RACE: Rapid Arterial Occlusion Evaluation scale; 3I-SS: 3-Item Stroke Scale; 95%: Hypothetical near-perfect test.

triage strategy is highly dependent on the interactions between all 3 time variables and the probability of LVO.

Evaluation of an alternative mRS distribution for the earliest successful EVT time had no effect on base case results, time thresholds, or relationships between variables previously described.

DISCUSSION

There is a pressing need to refine EMS triage strategies for acute ischemic stroke patients given the proven efficacy, yet limited availability, of EVT. Our base case analysis demonstrates an additional transportation time of 44 min to an ERH due to IRH bypass may be acceptable, more than double current American Stroke Association policy (15–20 min). However, caution is advised when interpreting this time threshold. Some populations may have a LVO rate closer to the lower end of our sensitivity analyses (8.7%), lowering the base case bypass threshold to 19 min (Figure 4B, Top) (32,46). Yet, even with this lower LVO rate, if the stroke onset to EMS triage interval was shorter (30 min for example), the bypass threshold would increase (to 56 min in this example) (Figure 4B, Top).

The ideal transportation destination depends on at least 3 clinically relevant interacting time variables: (1) onset to EMS triage interval, (2) ERH transportation time, and (3) IRH transportation time. No single variable can optimize triage, nor is there an absolute time difference between ERH and IRH transportation (i.e., bypass time) that would suffice for all stroke patients. These 3 time variables are known for any given patient at the time of EMS triage, so Figure 4 could be used to decide the optimal triage strategy, using a population's median probability of LVO. These data could be integrated into a mobile phone application, with times to area hospitals calculated automatically based on Global Positioning System data. As new trial data becomes available or treatment times improve, our model could easily be updated and pushed to this application, ensuring EMS providers have up to date guidance.

Our model suggests that harm may result from both false positives (LVO negative patient who is triaged to ERH and receives late IVT) and false negatives (LVO positive patient triaged to IRH who receives late EVT). Prehospital stroke scales, such as the C-STAT, can be used to predict the probability of LVO and reduce this harm. A highly sensitive test optimizes triage when the onset to EMS triage interval is short, while a highly specific test optimizes triage when this interval is long. Thus, a particularly intriguing strategy could be to use different discrimination thresholds for any given prehospital stroke scale to alternatively optimize sensitivity or specificity in response to the onset to EMS triage interval. Importantly, these tools do not require additional technology, making rapid, widespread implementation feasible. However, current test characteristics are based on retrospective studies of select hospital cohorts with varying definitions of LVO. The usability, reproducibility, sensitivity, and specificity of all tests may be significantly different when implemented in the prehospital environment. Prospective trials of prehospital triage strategies and scales are needed.

While differences in expected utility are small in the base case analysis, the magnitude of gains or losses between triage strategies are larger in a variety of alternate scenarios. For example, larger differences in outcomes occur when both the transportation time to the ERH and stroke onset to EMS triage interval are long (>0.6 QALYs) (Figure 4B, Top). In addition, due to the tremendous incidence of stroke in the United States, even a small improvement of 0.2 QALYs per stroke could result in a large overall public health benefit of ~100,000 QALYs. Because of the underlying uncertainty surrounding parameter values, the purpose of the model is to provide insights into the underlying forces that drive triage decisions, rather than focusing on precise time thresholds or specific gains in QALYs. Current clinical practice is based upon assumptions and biases that are often not transparent nor data-driven. Our model makes these assumptions and sources of data transparent, and then uses sensitivity analyses to explore the impact of parameter uncertainty.

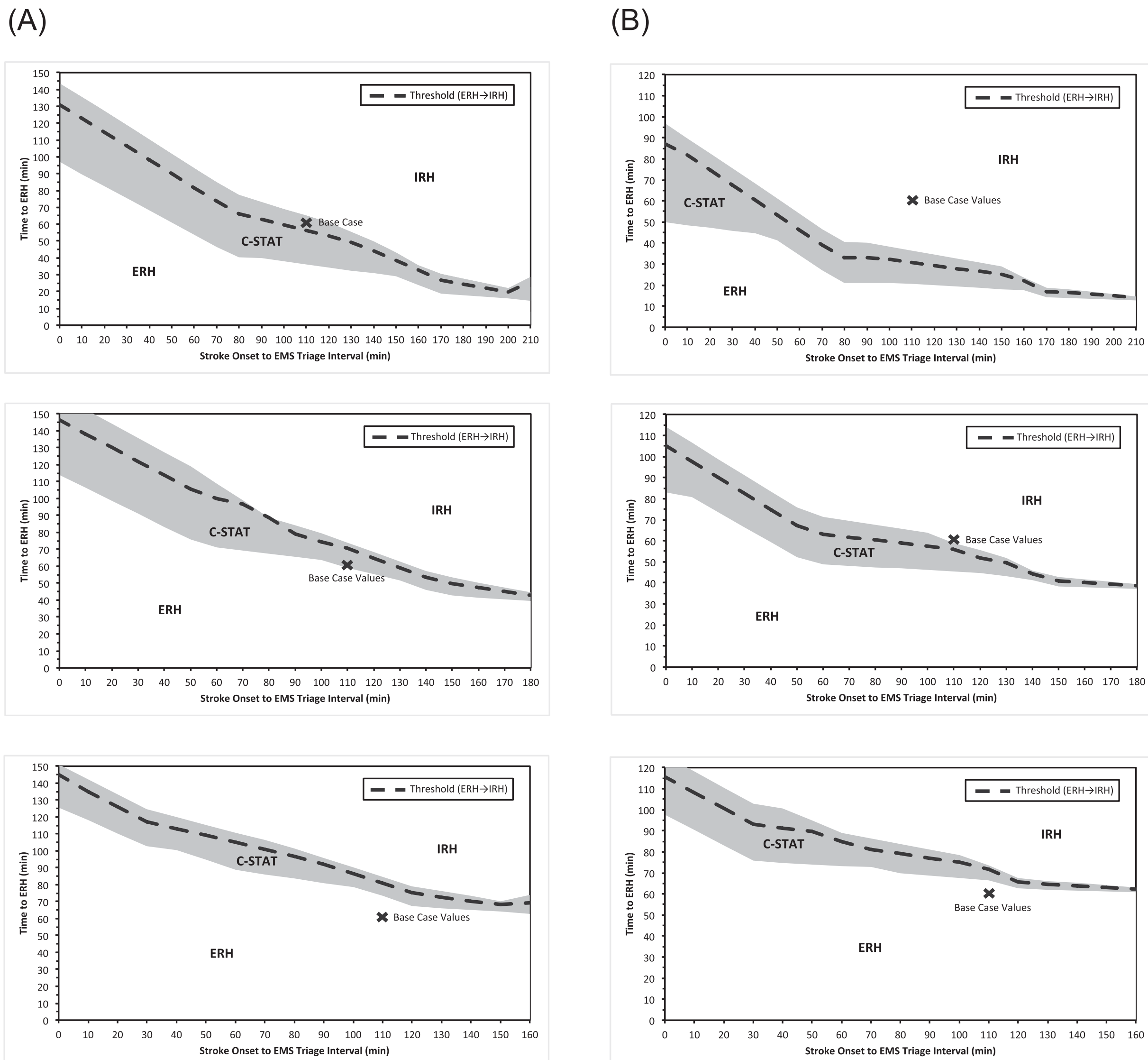


Figure 4. Two-way sensitivity analyses of stroke onset to emergency medical services (EMS) triage interval versus transportation time to the endovascular-ready hospital (ERH). Three intravenous tPA-ready hospital (IRH) transportation times and 2 probabilities of large vessel occlusion (LVO) were evaluated. Areas represent when each triage strategy is optimal: (1) transport to the IRH, (2) transport to the ERH, or (3) apply the Cincinnati Stroke Triage Assessment Tool (C-STAT) and transport to the ERH if positive. Dashed lines represent thresholds after excluding the C-STAT strategy.

Several limitations of our analysis should be noted. Parameter values were based on a detailed literature review to represent actual clinical practice, but variation between hospital systems was not captured by the model. Some hospital systems may have different door-to-needle times for IVT or different decision-to-completion times for EVT. Similarly, delays in transfer from an IRH to an ERH may differ depending on transportation vehicle proximity, and pre-notification during transfer may be used to reduce treatment times (23) Rates of endovascular reperfusion may also vary based on the device used or procedural expertise. Some systems use wider therapeutic windows for EVT or have different selection criteria. Uncertainty surrounding the effectiveness of EVT was also not addressed. However, changes to these system-level variables in the model would likely favor EVT due to greater experience with acute stroke care over time, thereby further decreasing the relative utility of transport to the nearest IRH. Thus, our model likely represents a conservative estimate of the potential benefit of direct transport to an ERH over an IRH. The model itself could easily integrate system-specific data.

Missed strokes and patients misdiagnosed with stroke were also not evaluated. Missed strokes would likely be transported to the closest hospital. As such, these patients would have no effect on the relative benefit of different stroke triage strategies, as triage never took place. Although early stroke recognition is critical, it falls outside the scope of this decision analysis. Patients misdiagnosed with stroke could be over-triaged to a higher-level facility. Although estimates vary, approximately 30% of EMS identified strokes are misdiagnosed (47,48). However, the clinical care of stroke mimics is generally either not time-dependent (e.g., complex migraine), or can be treated adequately in the prehospital setting (e.g., hypoglycemia). Therefore, longer transportation times are unlikely to cause significant morbidity. Including stroke mimics in the LVO rate would only dilute the observed effect of optimized triage and would not change the underlying importance of triage decisions for actual stroke patients.

Important factors that might influence system-wide implementation of this triage strategy have not been considered in the model. Recently published studies demonstrating efficacy for EVT in select patients with favorable CT perfusion imaging between 6 and 24 h after stroke onset were not addressed (49,50). Although important, these findings do not presently change EMS triage between 0 and 6 h, which was the scope of our analysis. Patients with specific contraindications for IVT were not addressed, as optimal prehospital management for this subgroups is less established (11). Similarly, hemorrhagic strokes were not addressed, as our understanding of the time-dependent clinical consequences of initial triage decisions for this subgroup is less robust. Resource limitations were also not evaluated. For example, if our model was implemented exactly as described, it would likely increase the number of patients transported directly to an ERH. This could overwhelm an ERH due to increased volume of acute neurologic patients, over-extend EMS resources with longer ERH transportation times, and worsen the skills of IRH personnel in delivery of acute stroke care due to decreased volume.

CONCLUSIONS

This decision analysis demonstrates that EMS stroke triage decisions regarding transport to the closest IRH versus direct transport to an ERH may have an impact on patient outcomes. No single absolute time difference between hospitals is capable of optimizing triage for all patients. Current American Stroke Association policy should be revisited, as the window for IRH bypass may be too narrow, and does not take into account interactions between time variables known to EMS. The C-STAT and other prehospital stroke scales may help optimize triage further.

ORCID

Justin L. Benoit http://orcid.org/0000-0002-0669-2963

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