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This article has been withdrawn from the *Journal of NeuroInterventional Surgery*.The editorial office has received an email from Dr Akash Kansagra, one of the authors, detailing multiple corrections in their data specifically pertaining to errors of over-representation in their simulation analysis. Although the authors have stated that these data errors do not alter the conclusions of their manuscript, the editorial board has withdrawn this paper and asked the authors to address these errors in a revision that would be subject to further peer review.

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ORIGINAL RESEARCH

Effect of routing paradigm on patient-centered outcomes in acute ischemic stroke

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ABSTRACT

Objective To compare performance of routing paradigms for patients with acute ischemic stroke using clinical outcomes.

Methods We simulated different routing paradigms in a system comprising one primary stroke center (PSC) and onecomprehensive stroke center (CSC), separated by distances representative of urban, suburban, and rural environments. In the Nearest Center paradigm, patients are initially sent to the nearest center, while in CSC First, patients are sent to the CSC. In Rhode Island and Distributive paradigms, patients with Field Assessment Stroke Triage for Emergency Destination (FAST-ED) score ≥4 are sent to the CSC, while others are sent to the nearest center or PSC, respectively. Performance and efficiency were compared using rates of good clinical outcome determined by type and timing of treatment using clinical trial data and number needed to bypass (NNB).

Results Good clinical outcome was achieved in 43.67% of patients in Nearest Center and 44.62% in CSC First, Rhode Island, and Distributive in an urban setting; 42.79% in Nearest Center and 43.97% in CSC First and Rhode Island in a suburban setting; and 39.76% in Nearest Center, 41.73% in CSC First, and 41.59% in Rhode Island in a rural setting. In all settings, the NNB was considerably higher for CSC First than for Rhode Island or Distributive.

Conclusion Routing paradigms that allow bypass of nearer hospitals for thrombectomy-capable centers improve population-level patient outcomes. Differences are more pronounced with increasing distance between hospitals; therefore, the choice of model may have greater effect in rural settings. Selective bypass, as implemented in Rhode Island and Distributive paradigms, improves system efficiency with minimal effect on outcomes.

INTRODUCTION

Earlier treatment of patients with acute ischemic stroke (AIS) is known to correlate with improved clinical outcomes,[1–3] underscoring the importance of rapid transport of these patients to hospitals capable of implementing appropriate care. When intravenous tissue plasminogen activator (IV tPA) was the only approved treatment for AIS, minimizing time to treatment generally implied routing the patient to the nearest capable center. However, with recent clinical trials demonstrating dramatic efficacy of endovascular thrombectomy (EVT) in patients with AIS due to large vessel occlusion (LVO),[2 3] routing of patients has become more complex. In particular, not all hospitals capable of administering IV tPA are capable of performing EVT. Optimal routing of patients by emergency medical services (EMS) must now account for these differences in treatment capability between hospitals.

Different routing models in use throughout the United States may prioritize initiation of either IV tPA or EVT based on initial hospital destination. For simplicity, we refer to hospitals capable of providing IV tPA but not EVT as primary stroke centers (PSCs) and hospitals that can provide both as comprehensive stroke centers (CSCs). So-called 'drip and ship' models prioritize early initiation of IV tPA at the closest center but delay EVT for patients who must be transferred to a CSC. In contrast, so-called 'mothership' models prioritize direct transport to a CSC for early initiation of EVT, potentially delaying administration of IV tPA owing to the longer transport time.[4] Although there are strong opinions regarding the optimal model for patient routing, objective, outcome-based data to guide the choice between these and related routing paradigms are scarce.

In this study, we develop a population-level simulation based on parameters derived from clinical trial data to model the effect of different EMS routing strategies on patient-centered clinical outcomes and underlying performance metrics, including the rate of functional independence at 90 days, time between symptom onset and important care points (eg, initial hospital arrival, IV tPA, and EVT), and the percentage of patients who receive IV tPA and EVT. We further compare the performance of these routing strategies under different geographical conditions corresponding to urban, suburban, and rural settings. We hypothesize that models that include a mechanism for hospital bypass will outperform those that do not, and that the choice of routing paradigm will have the greatest effect in rural areas, where separation between hospitals is large.

METHODS

Model design

Using MATLAB R2017a Simulink (Mathworks, Natick, Massachusetts, USA), we created a hospital network model consisting of one PSC and one CSC. Both centers can administer IV tPA and perform non-invasive vascular imaging, but only the CSC can perform EVT. These two centers are separated by 10 miles in a simulated urban setting, 30 miles in a suburban setting, and 100 miles in a rural setting,

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with corresponding service radii of 15 miles, 45 miles, and 150 miles, respectively, around the PSC.

Patients with AIS are generated in a random location within the designated service area. The National Institutes of Health Stroke Scale (NIHSS), used as a measure of stroke severity, is generated probabilistically from an established distribution.[3] The presence of underlying LVO[5] and corresponding Field Assessment Stroke Triage for Emergency Destination (FAST-ED) score[6]—representative of prehospital stroke severity scales used by EMS as a surrogate for NIHSS—is also generated probabilistically based on the NIHSS. Symptom onset to time of EMS discovery is generated from a previously reported distribution.[7] Travel time to and between hospitals is determined by straight-line distance. Additional details are provided in the online supplement.

EMS routing paradigms

Each patient generated as above is replicated and assigned to each EMS routing paradigm being tested. The initial hospital destination is chosen according to one of four models for EMS routing:

1. *Nearest Center:* Patients are sent to the nearest center (PSC or CSC), regardless of stroke severity.
2. *CSC First:* Patients are sent to the CSC, regardless of stroke severity.
3. *Rhode Island:* Patients with FAST-ED score ≥4 are sent to the CSC, while patients with FAST-ED score <4 are sent to the nearest center (PSC or CSC). This approach is similar to the paradigm used in Rhode Island[8] and is a hybrid of 'Nearest Center' and 'CSC First' models, with the latter being used in patients with greater likelihood of underlying LVO.
4. *Distributive:* Patients with FAST-ED score ≥4 are sent to the CSC, while patients with FAST-ED score <4 are sent to the PSC. This approach is intended to ensure EVT access for patients with LVO by diverting patients with low-severity strokes to a PSC, and is therefore feasible only in urban settings where bypass of a nearby CSC in favor of a more distant PSC does not incur a large time penalty.

While these routing models determine the initial hospital destination, EVT-eligible patients at a PSC may be subsequently transferred to a CSC as needed in all models.

Deterministic simulation

Additional factors that influence choice of treatment or treatment-related outcomes, such as presence of contraindications to IV tPA and/or EVT, rate of LVO recanalization with IV tPA and/or EVT, and development of intracranial hemorrhage (ICH), are based on best estimates derived from clinical trial data (table 1).[3 9–12]

Good clinical outcome is defined as a 90-day modified Rankin Scale (mRS) of 0–2 and determined by type of treatment received and time to treatment. Patients without LVO may receive IV tPA or no treatment, with corresponding time-dependent mRS distributions from the treatment and placebo arms of a pooled analysis of IV tPA-related clinical trial data.[13] Similarly, patients with LVO may receive no treatment, IV tPA only, or EVT with or without IV tPA. The mRS distributions correspond to the control arms of groups ineligible and eligible for IV tPA[2] and the time-dependent pooled intervention group achieving substantial reperfusion,[3] respectively, in a meta-analysis of EVT-related clinical trial data. Patients who do not achieve successful reperfusion

Table 1 Model parameters

Hospital environments			
	Urban	**Suburban**	**Rural**
Distance between CSC and PSC (miles)	10	30	100
Radius of hospital service (miles)	15	45	150
System constraints			
IV tPA treatment window[13] (hours)	4.5		
EVT treatment window[3] (hours)	7.3		
FAST-ED cut-off point for triage of patients with possible LVO[6]	4		
Minimum NIHSS threshold for EVT[2]	6		
Performance parameters			
	Deterministic model	**Stochastic model (triangle distribution)**	
	Value	**Minimum**	**Maximum**
PSC door-to-needle time[23] (min)	60	50	100
CSC door-to-needle time[24] (min)	40	30	60
CSC needle-to-puncture time[2] (min)	60	30	90
CT angiography[2] (min)	15	10	30
Transfer lag[2] (min)	50	30	70
Probability of IV tPA ineligibility[9] (%)	10.1	6.1	14.1
Probability of EVT ineligibility[3] (%)	11.2	8.7	13.7
Probability of a LVO achieving recanalization with IV tPA alone[10 11] (%)	18	14	22
Probability of ICH from IV tPA[12] (%)	6	3	9
Probability of successful reperfusion after EVT[3] (%)	80	65	95

CSC, comprehensive stroke center; EVT, endovascular thrombectomy; FAST-ED, Field Assessment Stroke Triage for Emergency Destination; ICH, intracranial hemorrhage; IV tPA, intravenous tissue plasminogen activator; LVO, large vessel occlusion; NIHSS, National Institutes of Health Stroke Scale; PSC, primary stroke center.

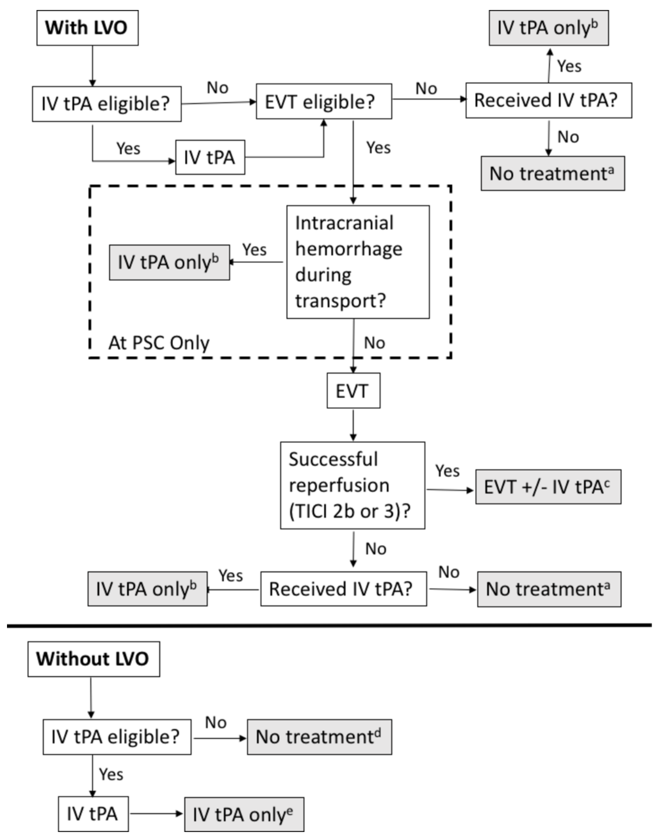

Figure 1 Flow diagram depicting clinical care pathways for patients with and without LVO. The final mode of care (no treatment, IV tPA only, EVT ± IV tPA) determines the distribution used to generate modified Rankin Scale. Distributions based on control populations in [a]alteplase ineligible and [b]subgroup receiving alteplase in Goyal *et al*[2]; [c]EVT subgroup with substantial reperfusion in Saver *et al*[3]; [d]placebo and [e]alteplase subgroups in Lees *et al*.[13] EVT, endovascular thrombectomy; IV tPA, intravenous tissue plasminogen activator; LVO, large vessel occlusion; PSC, primary stroke center; TICI, Thrombolysis in Cerebral Infarction.

after EVT, defined as reperfusion grades of Thrombolysis in Cerebral Infarction 2b or greater, are assigned clinical outcomes as if they did not receive EVT, using the distribution for either 'no treatment' or 'IV tPA only,' as appropriate. This simplifying assumption is necessary owing to a lack of pertinent clinical trial data. The 'IV tPA only' distributions used for the LVO and non-LVO groups both included patients with ICH. A schematic depicting this outcome assignment is shown in figure 1.

Stochastic simulation

To account for uncertainty and variability associated with deterministic model parameters,[14] we also created a stochastic model that is identical to the deterministic model except that fixed parameter estimates are replaced by probability distributions encompassing a realistic range of parameter values (Table 1). For each such parameter, a triangular probability distribution is used, with the peak of the distribution corresponding to the fixed parameter estimate used in the deterministic model, and the bounds of the probability distribution corresponding to two SD or reasonable estimates based on local institutional experience. SDs are determined using the binomial distribution for counting data and reported SD for continuous data when available.

Simulation output and analysis

A deterministic simulation was performed to model the care of 100 000 patients. Measures of system performance (eg, time to treatment) and clinical outcome (eg, percentage of patients with good clinical outcome) were assessed for all routing models. The number needed to bypass (NNB)—defined as the percentage of patients initially taken to a non-nearest hospital divided by the percentage difference in rates of good clinical outcome between the route of interest and *Nearest Center*—was calculated as a measure of bypass efficiency. Subsequently, a stochastic simulation was performed to model the care of 10 000 patients in each of 1000 different sets of probabilistically generated model parameters. Rates of good clinical outcome and NNB for each trial were aggregated into distributions, which were used, in turn, to generate stochastic estimates of system performance and efficiency. Overall supremacy of routing paradigms was also quantified by determining the percentage of simulations for which each model achieved the best performance of all paradigms.

Approval of the institutional review board and informed consent were not required as no patients were involved in this study.

RESULTS

Deterministic model

Metrics of system performance in the deterministic model are described in table 2. As expected, Nearest Center has the shortest median time to first hospital arrival and highest rates of IV tPA administration, while CSC First has the highest rates of EVT.

Good clinical outcome was achieved in 44.04% in Nearest Center, 44.92% in CSC First, 44.92% in Rhode Island, and 44.92% in Distributive in an urban setting; 43.12% in Nearest Center, 44.33% in CSC First, and 44.33% in Rhode Island in a suburban setting; and 40.17% in Nearest Center, 42.16% in CSC First, and 41.98% in Rhode Island in a rural setting.

NNB was 75.53 for CSC First, 35.34 for Rhode Island, and 34.11 for Distributive in an urban setting; 55.17 for CSC First and 24.43 for Rhode Island in a suburban setting; and 33.42 for CSC First and 14.65 for Rhode Island in a rural setting.

Stochastic model

Metrics of system performance in the stochastic model are described in table 3. Good clinical outcome was achieved in 43.67% in Nearest Center, 44.62% in CSC First, 44.62% in Rhode Island, and 44.62% in Distributive in an urban setting; 42.79% in Nearest Center, 43.97% in CSC First, and 43.97% in Rhode Island in a suburban setting; and 39.76% in Nearest Center, 41.73% in CSC First, and 41.59% in Rhode Island in a rural setting.

NNB was 72.14 for CSC First, 33.07 for Rhode Island, and 33.06 for Distributive in an urban setting; 55.27 for CSC First and 23.98 for Rhode Island in a suburban setting; and 33.76 for CSC First and 14.10 for Rhode Island in a rural setting.

In an urban setting, CSC First, Rhode Island, and Distributive won 100.0%, 99.4%, and 67.6% of simulations, respectively. In a suburban setting, CSC First and Rhode Island won 100.0% and 99.3%, respectively. In a rural setting, CSC First won 100.0% of simulations and Rhode Island won 0%. In all three settings, Nearest Center won 0% of simulations.

DISCUSSION

We simulated the effects of different EMS routing models in a population of patients with AIS in order to derive objective

Table 2 Performance of deterministic simulation with 100 000 patients

	Nearest Center	CSC First	Rhode Island	Distributive
Urban				
Median time to first hospital arrival (min)	12.75 (7.85, 219.82)	18.18 (11.42, 224.03)	17.58 (11.03, 223.36)	17.64 (11.26, 223.53)
Median time to IV tPA (min)	73.55 (52.30, 85.62)	54.56 (49.69, 60.77)	54.86 (49.78, 61.86)	55.41 (50.17, 62.65)
Median time to EVT (min)	203.89 (129.62, 211.15)	131.33 (123.96, 148.04)	131.35 (123.97, 148.92)	131.36 (123.98, 149.27)
Patients receiving IV tPA (%)	68.49	68.38	68.39	69.39
Patients receiving EVT (%)	47.28	48.16	48.15	48.15
Patients undergoing interhospital transfer (%)	31.17	0	0.05	0.08
Patients initially taken to non-nearest hospital (%)	0	66.47	39.10	30.02
Patients with 90-day mRS 0–2 (%)	44.04	44.92	44.92	44.92
Number needed to bypass	–	75.53	35.34	34.11
Suburban				
Median time to first hospital arrival (min)	38.13 (23.44, 239.00)	54.30 (34.15, 253.59)	52.50 (32.98, 252.62)	–
Median time to IV tPA (min)	91.69 (73.07, 108.86)	83.29 (68.80, 101.41)	83.44 (68.94, 101.31)	–
Median time to EVT (min)	239.08 (155.92, 259.46)	160.86 (141.93, 187.87)	160.93 (141.94, 187.97)	–
Patients receiving IV tPA (%)	68.02	67.72	67.74	–
Patients receiving EVT (%)	45.21	46.28	46.28	–
Patients undergoing interhospital transfer (%)	29.44	0	0.05	–
Patients initially taken to non-nearest hospital (%)	0	66.76	29.56	–
Patients with 90-day mRS 0–2 (%)	43.12	44.33	44.33	–
Number needed to bypass	–	55.17	24.43	–
Rural				
Median time to first hospital arrival (min)	126.35 (77.81, 305.02)	179.26 (113.34, 340.63)	173.11 (109.53, 336.64)	–
Median time to IV tPA (min)	161.45 (120.16, 197.86)	180.71 (133.82, 235.32)	178.48 (131.65, 230.78)	–
Median time to EVT (min)	356.27 (235.76, 412.89)	259.77 (207.85, 323.66)	259.86 (207.90, 323.84)	–
Patients receiving IV tPA (%)	66.73	65.33	65.44	–
Patients receiving EVT (%)	41.36	42.34	42.34	–
Patients undergoing interhospital transfer (%)	26.60	0	0.05	–
Patients initially taken to non-nearest hospital (%)	0	66.51	26.52	–
Patients with 90-day mRS 0–2 (%)	40.17	42.16	41.98	–
Number needed to bypass	–	33.42	14.65	–

Parentheses denote IQR (25%, 75%).
CSC, comprehensive stroke center; EVT, endovascular thrombectomy; IV tPA, intravenous tissue plasminogen activator; mRS, modified Rankin Scale.

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metrics of system performance and patient-centered outcomes in different geographical settings. We found that the Nearest Center routing model—the only one that does not permit hospital bypass in any clinical circumstance—leads to the worst population-level clinical outcomes in urban, suburban, and rural settings, though a very small minority of patients may fare better under this model by presenting to a nearer hospital in time to receive IV tPA. While the CSC First routing model leads to the best population-level clinical outcomes, Rhode Island and Distributive—routing models that allow selective bypass—produce very similar outcomes with much greater bypass efficiency. Moreover, differences in system performance and clinical outcomes between competing routing models become more pronounced with increasing separation between the nearest PSC and nearest CSC, and therefore, the choice of paradigm may have the greatest effect in rural settings.

The optimal strategy for EMS routing has been the subject of active debate.[4] While there is widespread consensus that faster time to reperfusion confers considerable clinical benefit, there is growing, but not yet universal, agreement that hospital bypass—accelerating time to EVT while potentially delaying the initiation of IV tPA—is warranted in some cases. With this in mind, recently published guidelines from the Society of NeuroInterventional Surgery advocate primary transport to CSCs, diverting to a closer center only in specific situations.[15] Similarly, the American Heart Association/American Stroke Association (AHA/ASA) 'Mission: Lifeline Stroke' initiative introduced the severity-based stroke triage algorithm for EMS that recommends using stroke severity screening tools to identify patients with possible LVO to route directly to CSCs in a specific time and distance window.[16] However, the 2018 AHA/ASA Guidelines for Early Management of Stroke also recognize the importance of regional customizability and acknowledge the lack of sufficient evidence to recommend a specific scale or bypass threshold, though they do suggest that hospital bypass that delays IV tPA administration by ≥15 min should be avoided.[17]

Conditional probabilistic models by Schlemm *et al*,[18] Holodinsky *et al*,[19] and Milne *et al*[20] have reinforced the importance of situational factors such as patient location, stroke severity, treatment times, and distance between PSC and CSC on patient outcomes, and use this approach to compare the efficacy of the CSC First and Nearest Center models on a patient level to

Table 3 Performance of stochastic simulation with 10 000 patients for 1000 trials

	Nearest Center	CSC First	Rhode Island	Distributive
Percentage of patients with 90-day mRS 0–2: medians and interquartile ranges (%)				
Urban	43.67 (43.03, 44.47)	44.62 (43.96, 45.47)	44.62 (43.96, 45.47)	44.62 (43.95, 45.46)
Suburban	42.79 (42.16, 43.51)	43.97 (43.27, 44.75)	43.97 (43.27, 44.75)	–
Rural	39.76 (39.30, 40.27)	41.73 (41.18, 42.34)	41.59 (41.05, 42.21)	–
Percentage of simulations won or tied for win (%)				
Urban	0	100.0	99.4	67.6
Suburban	0	100.0	99.3	–
Rural	0	100.0	0	–
Percentage of patients initially taken to non-nearest hospital: medians and interquartile ranges (%)				
Urban	0	68.53 (61.87, 77.00)	31.42 (28.40, 35.53)	31.41 (27.86, 35.15)
Suburban	0	65.22 (55.12, 78.68)	28.30 (24.02, 33.83)	–
Rural	0	66.51 (59.11, 73.88)	25.80 (22.94, 29.27)	–
Number needed to bypass: medians and interquartile ranges				
Urban	–	72.14 (66.53, 77.00)	33.07 (30.54, 35.53)	33.06 (30.28, 35.50)
Suburban	–	55.27 (49.66, 63.45)	23.98 (21.64, 27.28)	–
Rural	–	33.76 (31.44, 35.69)	14.10 (13.11, 15.09)	–

Parentheses denote IQR (25%, 75%). CSC, comprehensive stroke center; mRS, modified Rankin Scale.

determine the best destination for an individual patient under specific conditions. Another model by Bogle *et al*[21] simulates the AHA/ASA algorithm in two counties in the United States. The reported outcomes focus on efficiency of routing by measuring overtriage and undertriage, and thus do not simulate changes in treatment and outcomes related to recanalization or ICH following IV tPA administration. Such research provides important insights for EMS providers and treating physicians, but individuals with the larger task of selecting an EMS routing paradigm for an entire region would be better served by insight into the population-level health impact of these models. Our approach aims to provide such insight while incorporating real-world factors that influence the treatment pathway and expected clinical outcome.

Proponents of the Nearest Center model note that bypassing a closer center can cause patients to miss the treatment window for IV tPA. Indeed, our simulation validates this concern by virtue of the smaller percentage of patients who receive IV tPA in the CSC First and Rhode Island models compared with the Nearest Center model. However, despite rendering a small minority of patients ineligible for IV tPA, EMS routing models that allow hospital bypass generally confer a substantial outcome benefit at a population level by shortening the time for EVT.

Overall, the relative performance of CSC First, Rhode Island, and Distributive for population-level outcomes is comparable. The Rhode Island and Distributive models are intermediate approaches to Nearest Center and CSC First paradigms that introduce a heuristic element based on clinical stroke severity in order to classify patients into groups with different probabilities of underlying LVO, which may be used as the basis for subsequent routing. We found that the CSC First paradigm produces the highest rates of good clinical outcome at a population-level in all settings, probably owing to the dramatic impact of interhospital transfer on time to treatment. However, Rhode Island and Distributive produce nearly identical outcomes to those of CSC First, but do so with much greater bypass efficiency. In particular, these paradigms use a clinical severity threshold to predict the presence of LVO and apply bypass selectively, thereby subjecting a smaller number of patients to bypass.

This analysis has some limitations. First, factors beyond the outcome measures reported here may influence the choice of routing model. For example, compared with the CSC First approach, the Rhode Island and Distributive models better distribute patient load between a PSC and CSC and thereby reduce resource strain at the CSC and maintain expertise at the PSC. Second, several model parameters are assumed to be independent of one another, which in some cases may overlook correlations between parameters. For example, the clinical outcome of a patient with LVO following recanalization is probably dependent on NIHSS.[22] Since clinical outcome distributions are taken from clinical trial data, this percentage currently does not vary with NIHSS in our model. These simplifying assumptions are necessary in the absence of high-level clinical trial data to inform these interdependencies. Finally, eligibility for EVT or IV tPA was determined based on exclusion criteria from high-level clinical trial data, or equivalently, evidence-based guidelines in use at the time, but clinical practice may deviate from a strictly trial-based or guidelines-based approach at some sites. Nevertheless, this limitation affects all routing models and may not meaningfully affect their relative performance.

CONCLUSION

EMS routing models that allow at least some degree of bypass consistently yield better population-level outcomes than a Nearest Center approach. Paradigms that allow selective bypass of patients with a high probability of LVO yield similar outcomes as CSC First, but with much greater bypass efficiency. The magnitude of performance discrepancy is greatest when separation between hospitals is large. Head-to-head comparisons between different EMS routing models in the same population are improbable in the real world, and thoughtful, informed simulation can therefore quantitatively inform the choice of EMS routing paradigm and associated triage policies in a variety of settings.

Contributors MHZ made substantial contribution to design and construction of the work, acquisition and analysis of data, drafting and revising, approved the final version, and agrees to be accountable. APK made substantial contribution to

conception and design of the work, analysis and interpretation of data, drafting and revising, approved the final version, and agrees to be accountable.

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