SUPPLEMENTAL MATERIAL

A Decision Analysis Model for Pre-hospital Triage of Patients with Acute Stroke

Yaqian Xu, MD; Neal S. Parikh, MD; Boshen Jiao, MPH; Joshua Z. Willey, MD, MS; Amelia K. Boehme, PhD; Mitchell S. V. Elkind, MD, MS

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Table I. Assumptions for time-independent probabilities and time-dependent probabilities and formulae

Variable name	Description	Probability/ Formula	Notes
Key time-independent probabilities			
Pel	P of not having IV-tPA contraindication within the 4.5 hour window	0.35	This probability accounts for contraindications and real-world reasons for IV-tPA withholding in the 3 hour window, including ICH/SAH and rapidly improving or mild stroke.[1]
Ptpa1	P of receiving IV-tPA treatment among those without contraindication	0.82	As seen in 2010-2011 in Get With The Guidelines-Stroke analysis.[1]
Ptpa	P of receiving IV-tPA (=Pel*Ptpa1)	0.287	
Plvo	P of LVO in absence of screening; prevalence estimate no. 1	0.0487	Percentage of LVO among all suspected stroke patients from a real-world EMS study in North Carolina.[2]
	P of LVO in absence of screening; prevalence estimate no. 2	0.118	Percentage of LVO among all AIS codes (including transient ischemic stroke) in West Virginia.[3]
	Screened negative	Negative omission rate ranges	Derived from combinations of LVO prevalence and sensitivity/specificity of LVO scales using Bayes theorem
	Screened positive	Positive predictive value ranges	Derived from combinations of LVO prevalence and sensitivity/specificity of LVO scales using Bayes theorem
Pendo	P of endovascular therapy eligibility among LVO patients	0.865	Derived from data reported in a population-based estimate.[3]
Pearly	P of early reperfusion from IV-tPA among LVO patients	0.054	Based on percent without target occlusion at time of catheterization angiography in the HERMES collaboration study.[4]
Pre	P of substantial reperfusion in endovascular therapy	0.71	This rate of substantial reperfusion was reported in the HERMES collaboration study.[4]
Pgnp1	P of mRS0-1 in no LVO patients who did not receive tPA	0.4	Derived from percentage of mRS 0-1 in the placebo group with small-vessel occlusive stroke subtype in the NINDS trial.[5]
Pgnp2	P of mRS0-1 in LVO patients who did not receive tPA or endovascular therapy	0.25	Derived from weighted average of percentage of mRS 0-1 reported in the placebo group with large-vessel occlusive and cardioembolic stroke subtype in the NINDS trial.[5]
Time-dependent probabilities after IV-tPA, for patients without and with LVO			
No LVO, IV-tPA only			
	P of mRS 0-1 at onset-to-needle time of 15 min	0.63	Derived from reported percentage of mRS 0-1 in the IV-tPA group with small-vessel occlusive stroke subtype in the NINDS trial.[5]
	P of mRS 0-1 decline by 1 min delay in onset-to-needle time, 15-150 minutes	0.000731	Derived from the GWTG reported time-benefit curve decay variable for IV-tPA.[6]
	P of mRS 0-1 decline by 1 min delay in onset-to-needle time, 150-270 minutes	0.0003	Derived from the GWTG reported time-benefit curve decay variable for IV-tPA.[6]
Outcome	0-150 minute window 150-270 minute window	0.63- 0.00073*(to_n -15) 0.53- 0.0003*(to_n -150)	Derived from the GWTG reported time-benefit curve decay variable for IV-tPA.[6]

LVO, IV-tPA only			
	P of mRS 0-1 at onset-to-needle time of 15 min	0.389	Weighted average of percentage of mRS 0-1 in the IV-tPA group with large-vessel occlusive and cardioembolic stroke subtype in NINDS trial.[5]
	P of mRS 0-1 decline by 1 min delay in onset-to-needle time, 15-150 minutes	0.000731	Derived from the GWTG reported time-benefit curve decay variable for IV-tP.[6]
	P of mRS 0-1 decline by 1 min delay in onset-to-needle time, 150-270 minutes	0.0003	Derived from the GWTG reported time-benefit curve decay variable for IV-tPA.[6]
Outcome	0-150 minute window 150-270 minute window	0.63- 0.00073*(to_n -15) 0.53- 0.0003*(to_n -150)	Derived from the GWTG reported time-benefit curve decay variable for IV-tPA.[6]
Endovascular therapy, with early reperfusion from IV-tPA			
	P of mRS 0-1 at onset-to-puncture time of 180 min	0.394	Derived from results reported in the HERMES collaboration study.[4] Early reperfusion would be known at time of groin puncture, so the time of early reperfusion was set at the time of groin puncture.
Outcome	Time dependent probability of an excellent outcome	0.394- 0.00052*(to_evt -180)	Derived from results reported in the HERMES collaboration study.[4]
Endovascular therapy with substantial reperfusion from successful procedure			
	P of mRS 0-1 at onset-to-reperfusion time of 180 min	0.394	Derived from results reported in the HERMES collaboration study.[4]
Outcome	Time dependent probability of an excellent outcome	0.394- 0.00052*(to_evtr -180)	Derived from results reported in the HERMES collaboration study.[4]
Endovascular therapy without substantial reperfusion			
	P of mRS 0-1 at onset-to-puncture time of 120 min	0.222	Derived from results reported in the HERMES collaboration study.[4]
Outcome	Time dependent probability of an excellent outcome	0.222- 0.00052*(to_n -120)	Derived from results reported in the HERMES collaboration study.[4]

mRS, modified Rankin Scale; P, probability; LVO, large vessel occlusion.

Table II. Full-range of positive predictive values and false negative rates used in sensitivity analysis for probability of large vessel occlusion

LVO screening scales[7-10] *	Cutoff	Range†						
		Sensitivity	Specificity	Positive Likelihood Ratio (LR+)‡	LVO prevalence = 0.118		LVO prevalence = 0.0487	
					Positive Predictive Value (PPV)	False Negative Rate (FNR) §	Positive Predictive Value (PPV)	False Negative Rate (FNR) §
3I-SS	**≥4**	0.30-0.67	0.92-0.95	6.0-8.4	0.45-0.53	0.05-0.09	0.24-0.30	0.02-0.04
C-STAT	**≥2**	0.47-0.89	0.40-0.90	1.4-5.4	0.16-0.42	0.02-0.07	0.07-0.22	0.01-0.03
FAST-ED	**≥4**	0.61-0.70	0.88-0.89	5.5-5.8	0.43-0.44	0.04-0.06	0.22-0.23	0.01-0.02
LAMS	**≥4**	0.47-0.81	0.58-0.90	1.8-7.3	0.19-0.50	0.03-0.07	0.08-0.27	0.01-0.03
PASS	**≥2**	0.64-0.79	0.59-0.84	1.9-4.4	0.20-0.37	0.04-0.06	0.09-0.19	0.01-0.02
RACE	**≥5**	0.55-0.85	0.68-0.90	2.2-6.6	0.23-0.47	0.03-0.07	0.10-0.25	0.01-0.03
G-FAST	**≥3**	0.89	0.39	1.5	0.16	0.04	0.07	0.01
Overall		0.30-0.89	0.39-0.95	1.4-8.4	0.16-0.53	0.02-0.09	0.07-0.30	0.01-0.04

* 3I-SS, 3-item Stroke Scale; RACE, Rapid Arterial Occlusion Evaluation; LAMS, Los Angeles Motor Scale; FAST-ED, Field Assessment Stroke Triage for Emergency Destination; G-FAST, gaze-face-arm-speech-time score; PASS, Prehospital Acute Stroke Severity scale; C-STAT, Cincinnati Stroke Triage Assessment Tool; LVO, large vessel occlusion.

† Ranges for sensitivity and specificity were extracted from the AHA/ASA systematic review, and three other LVO screening scale validation studies published in 2017; positive predictive values and false negative rates were calculated using Bayes' theorem.

‡ Positive Likelihood Ratio (LR+) = Sensitivity/ (1- Specificity), represents how much the odds of the disease increase when a test is positive.

§ False Negative Rate (FNR) = 1- Negative Predictive Value, represents the probability of having false negatives.

Table III. Time variable inputs for base case

Variable name		Description	Ideal*	Data source	Real-world[11]†
Time spent outside of hospital					
temt		Onset to EMS arrival	10	Ten minutes was chosen simulate the most optimistic scenario of immediate alarm and response, given that the real-world time was reported as only 19 minutes.	19
tos		EMS time spent on scene	15	In the AHA/ASA 2018 stroke guideline, the median EMS time spent on scene was recommended to be within 15 minutes.[12]	15
ttrans		Scene to the closest PSC	20	We assumed that in the base case, the transport time from scene to the closest PSC is 20 minutes.	23
t1	temt+tos+ttrans	Onset to PSC arrival	45		57
t2	t3+tex	Transfer time from PSC to CSC	20	A plausible target, as reported by Felix et al using real-world EMS data.[13]	35
t3	t4-t1	Additional time if transported directly to CSC comparing with directly to PSC	20		6
tex		Detour time (difference in transport time between scene-PSC-CSC in drip-and ship and scene-CSC in mothership)	0	In the ideal scenario, we assumed that the PSC is located directly on the route to the CSC.	29
t4		Onset to CSC arrival in mothership	65		63
Time spent in hospital					
tp1		Door-to-needle time	35	Thirty-five minutes was chosen based on data reported from high-performing centers participating in randomized controlled trials,[4] which is shorter than the AHA/ASA target door-to-needle time of 60 minutes.[12]	36
tp2		Additional Door-to-needle time at PSC compared with CSC	0	In the ideal scenario, we assumed the same efficiency for PSCs and CSCs.	20
to		IV-tPA to PSC departure	10		47
tpr	tp1+tp2+to	Time spent at PSC (door-in-door-out)	45	We assumed the door-in-door-out time spent in the PSC was 45 minutes. This was derived from the target door-in-door-out time of 30 minutes in STEMI guidelines[14], modified to account for complexity of stroke evaluation and management.	103
to_n1	t1+tp1	Onset-to-needle time in drip-and-ship	80		113
to_n2	t4+tp1	Onset-to-needle time in mothership	100		99

te1		Door-to-puncture time in CSC in drip-and-ship	50	Derived from the median door-to-puncture time reported in the HERMES collaboration representing workflow time in high-performing stroke centers participating in clinical trials.[4]	57
tnp		Needle-to-puncture time in CSC in mothership	30	Derived from the median needle-to-puncture time reported in the HERMES collaboration representing workflow time in high-performing stroke centers participating in clinical trials.[4]	48
te2	tp1+tnp	Door-to-puncture time in CSC in mothership	65		84
tre2		Puncture-to-reperfusion time for endovascular therapy	30	Derived from the Recommendations from the Endovascular Stroke Standards Committee of the Society of Vascular and Interventional Neurology (SVIN).[15]	37
Drip-and-ship					
	t1+tpr+t2	Onset to CSC arrival in drip-and-ship	110		195
to_evt1	t1+tpr+t2+te1	Onset-to-puncture time for endovascular therapy	160		252
to_evtr1	t1+tpr+t2+te1+tre2	Onset-to-reperfusion time for endovascular therapy	190		289
Mothership					
to_evt2	t4+tp1+tnp	Onset-to-puncture time for endovascular therapy	130		147
to_evtr2	t4+tp1+tnp+tre2	Onset-to-reperfusion time for endovascular therapy	160		184

EMS, emergency medical services; LVO, large vessel occlusion; PSC, primary stroke center; CSC, comprehensive stroke center; STEMI, ST-Elevation Myocardial Infarction.
*All ideal time metrics were derived from guidelines or data reported from high-performing stroke centers that participated in clinical trials.
†All real-world time metrics were derived from the STRATIS registry, except for the EMS time spent on scene for which the AHA/ASA target time spent on-scene was assumed.

Table IV. Selected time thresholds for mothership to be the preferred strategy in an analysis with onset to EMS arrival time of 60 minutes, under real-world time metrics*

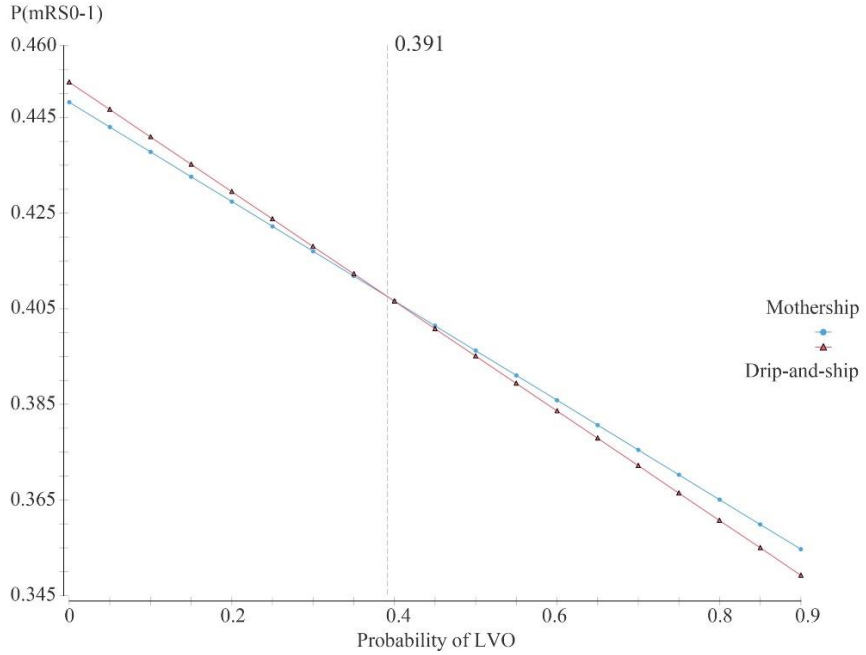
	LVO Prevalence = 0.0487		LVO Prevalence = 0.118	
LVO screening methods	**Probability of LVO**	**Additional transport time to CSC (min)**	**Probability of LVO**	**Additional transport time to CSC (min)**
Screened "-"[16] †	0.02	<28	0.06	<43
No Screening[2]	0.0487	<39	0.118	<63
Screened "+" ‡				
High sensitivity/ Low specificity[17]	0.07	<46	0.16	<77
Moderate sensitivity/ Moderate specificity[16]	0.18	<83	0.36	<135
Low sensitivity/ High specificity[18]	0.23	<99	0.45	<158

LVO, Large vessel occlusion; PSC, primary stroke center; CSC, comprehensive stroke center; EMS, emergency medical services.

* Onset to EMS arrival time was set at 60 minutes to account for longer onset to alarm time and longer EMS respond time.

† Probability of LVO calculated from using a single scale with moderate sensitivity (0.63), moderate specificity (0.85).

‡ We calculated positive predictive values across the full range of reported sensitivity/specificity, and chose to present 3 representative combinations: 1. high sensitivity (0.83), low specificity (0.40), and positive likelihood ratio (1.8); 2. moderate sensitivity (0.63), moderate specificity (0.85), and positive likelihood ratio (4.3); and 3. low sensitivity (0.30), high specificity (0.95), and positive likelihood ratio (6.0).



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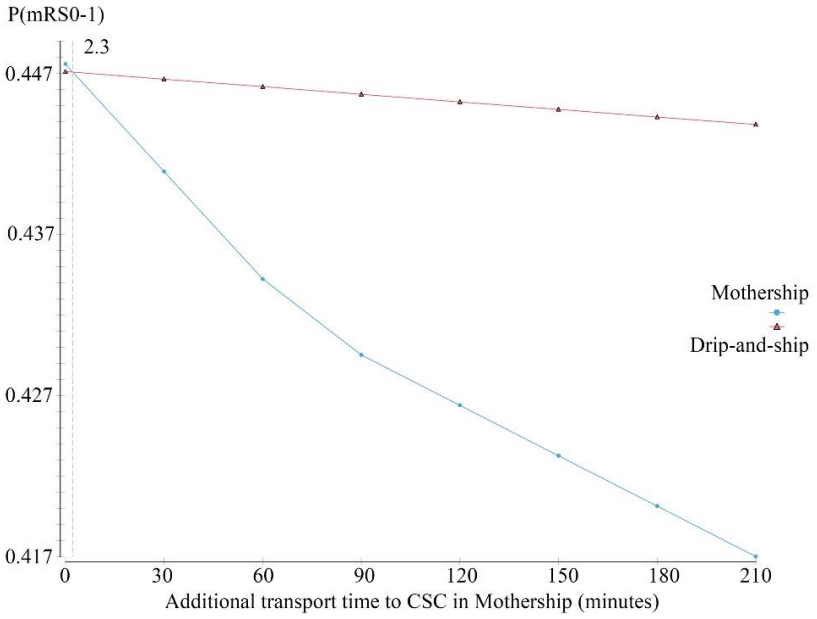
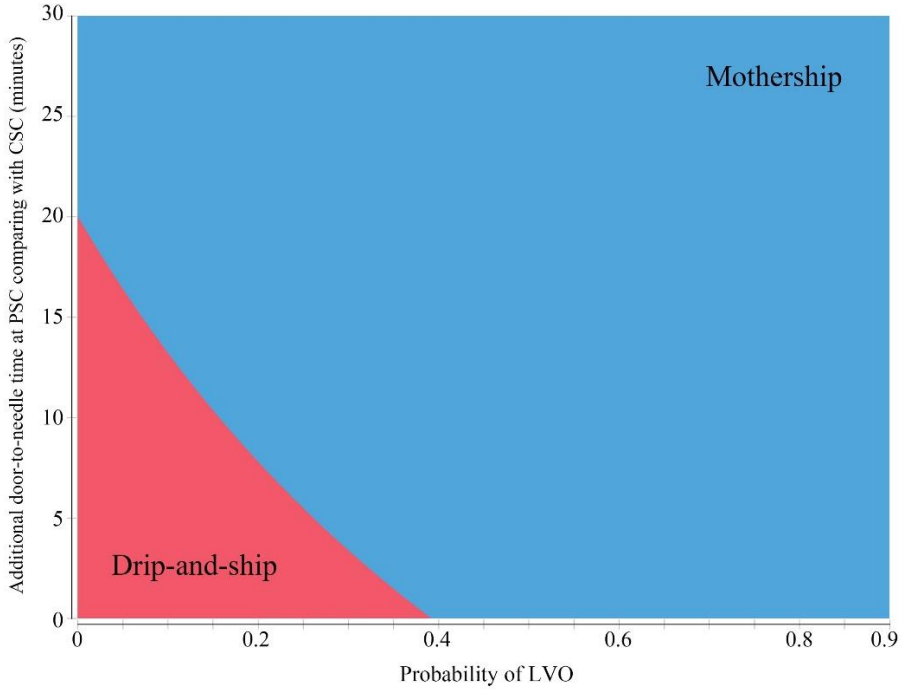


B.

Figure I. Selected one-way sensitivity analyses.

One-way sensitivity analyses were conducted by changing one variable at a time while holding all other variables constant using base case values. (**A)** one-way sensitivity analysis of probability of LVO (x-axis) and (**B)** one-way sensitivity analysis of additional travel time to CSC (x-axis). Y-axis: probability of a good outcome (mRS 0-1). Blue line indicates outcome from "Mothership"; Red line indicates outcome from "drip-and-ship". The higher line was chosen as the preferred triage strategy; the vertical line showed the threshold when the preferred strategy changed. LVO, large vessel occlusion; CSC, comprehensive stroke center; mRS, modified Rankin Scale.



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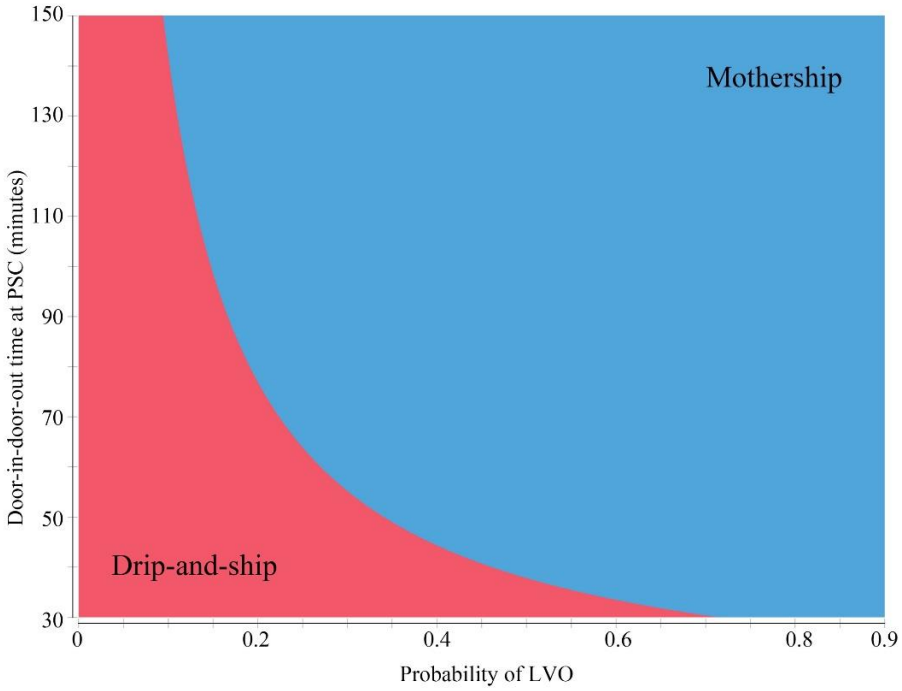

B.

Figure II. Selected Two-way sensitivity analyses.

Two-way sensitivity analyses were conducted by varying two variables simultaneously while holding all other variables constant using base case values. (**A)** X-axis: probability of LVO; y-axis: the additional door-to-needle time at the PSC compared with the CSC, minutes. (**B)** X-axis: probability of LVO; y-axis: the door-in-door-out time spent at the PSC. If variables of a case fall into the blue area, "mothership" is favored; if variables of a case fall into the red area, "drip-and-ship" is favored. LVO, large vessel occlusion; PSC, primary stroke center; CSC, comprehensive stroke center.

Supplemental Video Legend.

Video I. Results of the three-way sensitivity analysis.
Three-way sensitivity analysis of the base case was conducted by jointly varying transport time from scene to primary stroke center arrival (x-axis), additional travel time if taken directly to a comprehensive stroke center (y-axis), and the probability of a large vessel occlusion (LVO). The probability of LVO is on the z-axis, which is represented by time elapsed in the video. The left panel presents results from applying the ideal time metrics, and the right panel presents results from applying the real-world time metrics). The color of the area represents the favorable triage strategy in terms of anticipated clinical outcomes: blue represents favorability of the mothership approach, red represents favorability of the drip-and-ship approach, and gray represents patients outside of the IV-tPA treatment window who were not included in this model. LVO, large vessel occlusion; PSC, primary stroke center; CSC, comprehensive stroke center.

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