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RESEARCH ARTICLE

Neurologic Improvement in Acute Cerebral Ischemia

Frequency, Magnitude, Predictors, and Clinical Outcomes

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Abstract

Background and Objectives

Investigations of rapid neurologic improvement (RNI) in patients with acute cerebral ischemia (ACI) have focused on RNI occurring after hospital arrival. However, with stroke routing decisions and interventions increasingly migrating to the prehospital setting, there is a need to delineate the frequency, magnitude, predictors, and clinical outcomes of patients with ACI with ultra-early RNI (U-RNI) in the prehospital and early postarrival period.

Methods

We analyzed prospectively collected data of the prehospital Field Administration of Stroke Therapy–Magnesium (FAST-MAG) randomized clinical trial. Any U-RNI was defined as improvement by 2 or more points on the Los Angeles Motor Scale (LAMS) score between the prehospital and early post–emergency department (ED) arrival examinations and classified as moderate (2–3 point) or dramatic (4–5 point) improvement. Outcome measures included excellent recovery (modified Rankin Scale [mRS] score 0–1) and death by 90 days.

Results

Among the 1,245 patients with ACI, the mean age was 70.9 years (SD 13.2); 45% were women; the median prehospital LAMS was 4 (interquartile range [IQR] 3–5); the median last known well to ED-LAMS time was 59 minutes (IQR 46–80 minutes), and the median prehospital LAMS to ED-LAMS time was 33 minutes (IQR 28–39 minutes). Overall, any U-RNI occurred in 31%, moderate U-RNI in 23%, and dramatic U-RNI in 8%. Any U-RNI was associated with improved outcomes, including excellent recovery (mRS score 0–1) at 90 days 65.1% (246/378) vs 35.4% (302/852), $p < 0.0001$; decreased mortality by 90 days 3.7% (14/378) vs 16.4% (140/852), $p < 0.0001$; decreased symptomatic intracranial hemorrhage 1.6% (6/384) vs 4.6% (40/861), $p = 0.0112$; and increased likelihood of being discharged home 56.8% (218/384) vs 30.2% (260/861), $p < 0.0001$.

Discussion

U-RNI occurs in nearly 1 in 3 ambulance-transported patients with ACI and is associated with excellent recovery and decreased mortality at 90 days. Accounting for U-RNI may be useful for routing decisions and future prehospital interventions.

Trial Registration Information

clinicaltrials.gov. Unique identifier: NCT00059332.

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Glossary

ACI = acute cerebral ischemia; **ASPECTS** = Alberta Stroke Program Early CT Score; **ED** = emergency department; **IV t-PA** = IV tissue plasminogen activator; **LAMS** = Los Angeles Motor Scale; **LKW** = last known well; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **ROC** = receiver operator characteristic curve; **SICH** = symptomatic intracranial hemorrhage; **U-RNI** = ultra-early rapid neurologic improvement.

Rapid neurologic improvement (RNI) in the first hours after hospital arrival is a somewhat common occurrence in patients with acute cerebral ischemia (ACI). Between 5% and 24% of patients have been reported to show RNI in the first hours after arrival to the hospital.[1,2] Despite in-hospital RNI has been associated with generally more favorable course, a considerable proportion of these patients have disabled outcome at 3 months.[1-3]

To date, studies evaluating the causes, frequency, and outcomes of RNI have generally focused on RNI occurring after hospital arrival. RNI occurring in the prehospital period, when patients are under the observation of the emergency medical system personnel, has not been well delineated.

The temporal course of patient symptoms in the prehospital period has generally been ascertained only informally, often elicited from cognitively compromised patients and/or their lay relatives. Furthermore, in routine prehospital assessment practice, paramedics historically did not perform formal stroke severity rating scales. However, with the advent of direct routing of selected prehospital patients based on deficit severity to comprehensive stroke centers for potential endovascular therapy and the increasing performance of randomized trial of ACI treatment in the prehospital setting, further understanding of ultra-early RNI (U-RNI) in the prehospital and early postarrival period may aid in triaging patients to thrombectomy-capable hospitals and planning of ambulance-based intervention trials.[4-8]

The objectives of this study were to delineate the frequency, magnitude, predictors, and clinical outcomes of U-RNI among patients presenting to the EMS with ACI, comparing the initial neurologic assessment performed by paramedics with the one obtained after hospital arrival. The hypothesis of this study was that U-RNI among patients presenting with ACI was associated with more favorable outcomes.

Methods

We analyzed prospectively collected data of the Field Administration of Stroke Therapy–Magnesium (FAST-MAG) phase 3 trial, a randomized, placebo-controlled clinical trial of field-initiated magnesium sulfate in patients with hyperacute stroke within 2 hours after the last known well (LKW) time.[6] For this analysis, we included all enrolled patients with final diagnosis of acute cerebral ischemia (ACI), defined as patients with a final diagnosis of ischemic stroke or TIA with both a prehospital and early hospital arrival neurologic deficit score on the Los Angeles Motor Scale (LAMS) documented. All patients were examined in the field by paramedics, enrolled in the trial by explicit written informed consent or exception from informed consent in emergency circumstances, started on investigative agent prehospital, and transported to a study receiving hospital. Detailed methodology and statistical plan of the FAST-MAG trial have been previously published.[9,10] The study protocol was approved by the Institutional Review Board at each prehospital and hospital study site. As the study agent had neutral effects on outcome in the trial, the active and placebo groups were combined for this analysis.

Definition of Ultra-Early Rapid Neurologic Improvement

Ultra-early rapid neurologic improvement (U-RNI) was assessed using the Los Angeles Motor Scale (LAMS). The LAMS is a validated, 3-item prehospital scale for assessment of stroke severity, focused on motor deficits.[7-12] Facial droop is graded as absent (0 points) or present (1 point); arm drift as absent (0 points), drifts down (1 point), or falls rapidly (2 points); and grip strength as normal (0 points), weak grip (1 point), or no grip (2 points). On the LAMS, patients with unilateral weakness can score a maximum of 5 and patients with bilateral weakness a maximum of 10. LAMS scores correlate closely with concurrent NIH Stroke Scale (NIHSS) scores and predict functional outcomes with accuracy comparable to that of the NIHSS.[7] The LAMS items are a subsection of the Los Angeles Prehospital Stroke Scale (LAPSS), a stroke recognition screening tool[11-14] so that this instrument allows both rapid identification of patients with stroke and quantification of stroke severity in the field. For paramedics to call the FAST-MAG hotline for enrollment, symptoms needed to be present for a minimum of 15 minutes, and the patient had to have a primarily unilateral motor deficit (LAMS score 1–5).

A baseline, the prehospital LAMS was performed by paramedics in the field prior to patient enrollment. A subsequent LAMS was performed early after emergency department (ED) arrival (ED-LAMS) by certified FAST-MAG research investigators. Any U-RNI was defined as improvement by 2 or more points between the prehospital LAMS and ED-LAMS examinations and subclassified as moderate U-RNI (2–3 points) or dramatic U-RNI (4–5 points) improvement.

Outcome Measures

The primary outcome was excellent recovery, defined as a score of 0–1 on the modified Rankin Scale of global disability at 90 days. Additional 90-day outcomes included mortality

and neurologic deficit severity on the NIHSS. Early outcomes analyzed were NIHSS score at 24 hours; complete resolution of symptoms by 24 hours (time-defined TIA); 24-hour symptom resolution with the absence of cerebral infarction on neuroimaging (tissue-defined TIA)[15]; use of IV t-PA; symptomatic intracranial hemorrhage (SICH) by the fourth day of hospitalization; and ultra-early rapid neurologic deterioration, defined as worsening from prehospital LAMS to ED-LAMS score by ≥ 2 points, and discharge destination (home vs other).

Statistical Analysis

Bivariate—The *p* values for comparing ordered U-RNI vs categorical variables were computed using the nonparametric Wilcoxon rank-sum test, and the *p* values for binary any U-RNI (yes/no) vs categorical variables including binary outcomes were computed using the Fisher exact test. Odds ratios (ORs) and their 95% confidence bounds are reported. The *p* values for continuous variables vs ordered R-UNI were computed using the Spearman correlation allowing for ordinality and using the Kruskal-Wallis test ignoring ordinality.

Multivariable—Since all 4 outcomes are binary, adjusted ORs for U-RNI were computed using multiple logistic regression, controlling for covariates. Covariates were retained in the logistic model from a set of 17 candidate covariates using the Akaike Information Criterion (AIC). This does not necessarily give the same results as stepwise selection using *p* values. Model accuracy was assessed by computing the ROC area (=concordance statistic C) and the sensitivity and specificity at the maximum accuracy where accuracy is defined as accuracy = (sensitivity + specificity)/2. This is equivalent to the maximum Youden index.

Standard Protocol Approvals, Registrations, and Patient Consents

Participating sites included 40 emergency medical system agencies, 315 ambulances, and 60 acute care receiving hospitals in Los Angeles and Orange counties in CA. The study protocol was approved by the institutional review board at each prehospital and hospital study site. Enrollment occurred using explicit informed consent obtained via cellphone conversation between patients on the scene or their legally authorized representatives and enrolling physician-investigators off the scene or under exception from informed consent regulations. Clinical Trial Registration URL: clinicaltrials.gov. Unique identifier: NCT00059332.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

Among the 1,246 patients with final diagnosis of ACI, prehospital and early hospital arrival LAMS scores were available for 1,245. Among these patients, the mean age was 70.9 years (SD = 13.2), 45% were women, and the initial median prehospital LAMS was 4 (interquartile range [IQR] 3–5). The median LKW to prehospital LAMS examination time was 24.0 minutes (IQR 14.0, 42.0 minutes); the median LKW to ED-LAMS examination time was 59 minutes (IQR 46–80 minutes); the median prehospital LAMS to ED-LAMS examination time was 33 minutes (IQR 28–39 minutes).

Frequency and Magnitude

Overall, between the paramedic prehospital assessment and the early ED stroke severity assessment, 31% (384/1,245) of the patients with ACI exhibited any U-RNI, including 23% (289/1,245) with moderate and 8% (95/1,245) with dramatic RNI.

Figure 1 provides a granular representation of the frequency of changes of different magnitudes in stroke severity from prehospital LAMS to ED-LAMS. Overall, 39.4% (491/1,245) showed the most common course, no change in the LAMS score, whereas 7% (90/1,245) of patients showed ultra-early rapid neurologic deterioration of 2 or more points. Figure 2 illustrates the positive correlation between the LAMS change (the difference between the ED and the prehospital LAMS scores) vs NIHSS score at admission.

Clinical Characteristics

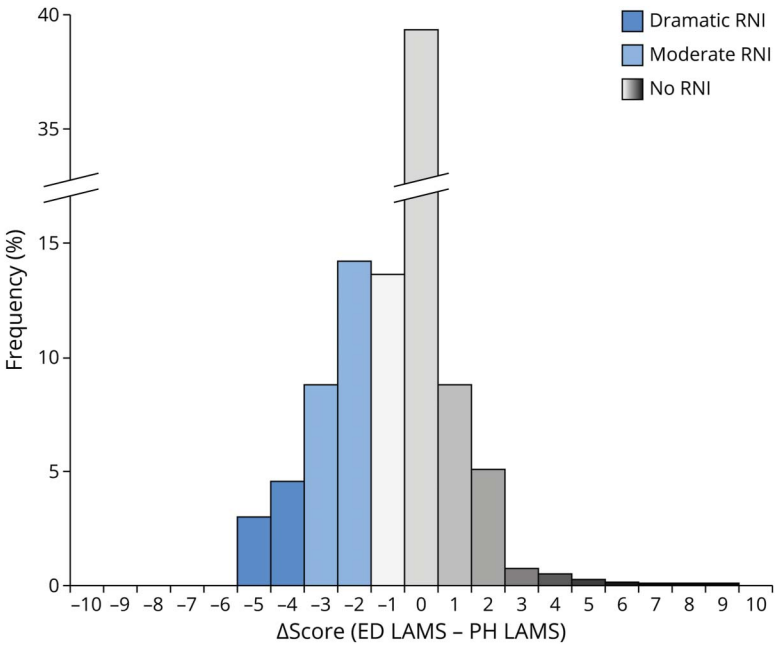
Demographics and baseline clinical characteristics of patients with any U-RNI, moderate U-RNI, dramatic U-RNI, and no U-RNI are shown in Table 1. Compared with patients with no U-RNI, patients with U-RNI had less diabetes, less atrial fibrillation, less history of coronary artery disease, more alcohol use, lower prehospital and early ED-LAMS scores, lower early ED NIHSS, and less frequent use of IV t-PA. U-RNI patients also tended to have mildly shorter intervals from prehospital LAMS to ED-LAMS.

Outcomes

Table 2 shows the bivariate relations between U-RNI and outcomes. Compared with the no U-RNI group, the occurrence of any U-RNI was statistically associated with all outcomes including more frequent excellent recovery (mRS score 0–1) at 90 days 65.1% (246/384) vs 35.4% (302/861), $p < 0.0001$, reduced mortality at 90 days 3.7% (14/384) vs 16.4% (140/861) $p < 0.0001$, and reduced frequency of SICH 2.1% (6/384) vs 4.6% (40/861). Any U-RNI had less severe NIHSS neurologic deficit at both 24 hours and 90 days, more frequent final diagnosis of TIA (rather than ischemic stroke), less frequent postarrival neurologic deterioration, shorter length of stay, and more frequent discharge disposition to home.

Despite the generally improved outcomes with any U-RNI, a relatively high proportion of U-RNI patients had poor clinical outcomes. At the time of discharge, 1.3% (5/384) of any U-RNI were expired vs 5.9% (51/861) with no U-RNI, 43.2% (166/384) vs 69.8% (601/861) were discharged to a location other than home, including 3.9% (15/384) vs 8% (69/861) to a skilled nursing facility, 2.6% (10/384) vs 4.6% (40/861) to subacute rehab, and 12.2% (47/384) vs 22.3% (192/861) to acute rehab. At 90 days, dead (mRS score = 6) outcome occurred in 3.6%

Figure 1 Frequency of Changes of Different Magnitudes in Los Angeles Motor Scale Score From Prehospital to Emergency Department



Bar chart shows the frequency of all changes (improvement, neutral, and worsening). Dramatic ultra-rapid neurologic improvement (U-RNI) patient bars are dark blue, moderate U-RNI patient bars are light blue, and no U-RNI patient bars are light gray. As the delta score is measured by subtracting the emergency department Los Angeles Motor Scale (LAMS) from the prehospital LAMS, negative values indicate improvement, and positive values indicate worsening.

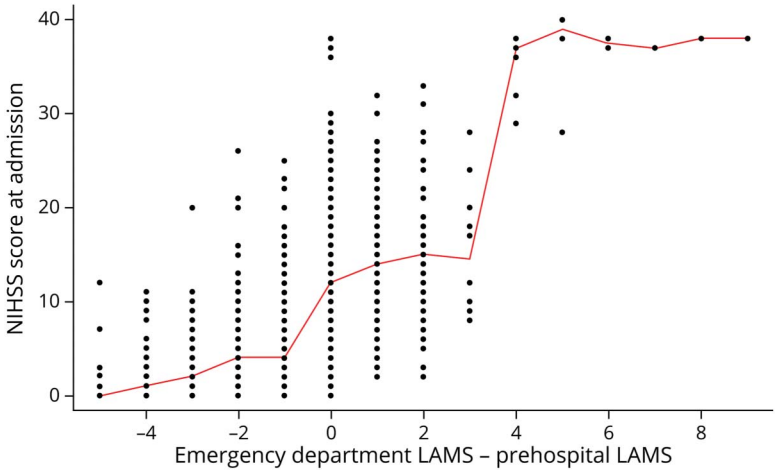
(14/384) of any U-RNI, 4.6% (13/289) of moderate U-RNI, and 1.1% (1/95) of dramatic U-RNI patients.

In multivariate analyses, both moderate and dramatic U-RNI (Table 3) were simultaneously associated with more frequent excellent recovery (mRS score 0–1) at 90, increased survival to 90 days, reduced SICH, and discharge disposition to home. More favorable ASPECTS score, less diabetes or lower glucose level at presentation, and fewer IV t-PA treatments were also generally independently associated with better outcomes.

Discussion

In this study, rapid neurologic improvement among ambulance-transported patients with acute cerebral ischemia, evaluated ultra-early using serial LAMS examinations between time of paramedic encounter and immediately post-ED arrival, and prior to any treatment intervention (IV t-PA and/or endovascular treatment), was frequent, occurring in nearly 1 in 3 patients. U-RNI was moderate in nearly 4 in 10 patients and dramatic in nearly 1 in 10.

Figure 2 Correlation of Los Angeles Motor Scale Score Change From Prehospital to Emergency Department With NIH Stroke Scale Score at Hospital Admission



Scatterplot of the Los Angeles Motor Scale score LAMS change (emergency department LAMS–prehospital LAMS) vs NIH Stroke Scale score at admission. The LAMS change ranges from a 5-point improvement (decrease) to a 9-point worsening (increase); the scatter plot illustrates the positive correlation: Spearman correlation = 0.647, $p < 0.001$; red line connects medians.

Table 1 Baseline Characteristics of the Field Administration of Stroke Therapy–Magnesium (FAST-MAG) Trial Acute Cerebral Ischemia Cohort (N = 1,245)

Acute cerebral ischemia cohort (N = 1,245, 100%)	Any U-RNI (N = 384)	Moderate U-RNI (N = 289)	Dramatic U-RNI (N = 95)	No U-RNI (N = 861)	*p* Value, 3-way comparison	*p* Value, 2-way any vs no RNI	*p* Value, 2-way dramatic vs no RNI
Age (y, mean [SD])	70.0 (±13.0)	72.0 (±12.9)	67.7 (±13.1)	70.9 (±13.2)	0.02	0.96	0.03
Women (n, %)	176 (45.8%)	137 (47.4%)	39 (41.1%)	388 (45.1%)	0.94	0.80	0.46
Race (n, %)					0.33	0.15	0.37
White and Hispanic	312 (81.3%)	239 (82.7%)	73 (76.8%)	660 (76.7%)			
Black	41 (10.7%)	23 (8.0%)	18 (18.9%)	127 (14.8%)			
Asian	30 (7.8%)	26 (9.0%)	4 (4.2%)	65 (7.6%)			
Other	1 (0.3%)	1 (0.3%)	0 (0%)	9 (1.0%)			
Hispanic or Latino (n, %)	83 (21.6%)	67 (23.2%)	16 (16.8%)	170 (19.7%)	0.31	0.45	0.50
Hypertension (n, %)	290 (75.5%)	227 (78.5%)	63 (66.3%)	675 (78.4%)	0.13	0.26	0.008
Diabetes (n, %)	71(18.5%)	60 (20.8%)	11 (11.6%)	214 (24.9%)	0.007	0.01	0.004
Hyperlipidemia (n, %)	191 (49.7%)	152 (52.6%)	39 (41.1%)	441 (51.2%)	0.43	0.63	0.06
Atrial fibrillation (n, %)	89 (23.2%)	70 (24.2%)	19 (20.0%)	245 (28.5%)	0.04	0.05	0.08
Myocardial infarction (n, %)	31 (0.1%)	26 (9.0%)	5 (5.3%)	118 (13.7%)	0.01	0.005	0.02
Tobacco use (n, %)	68 (17.7%)	48 (16.6%)	20 (21.1%)	151 (17.5%)	0.82	0.94	0.40
Current alcohol use (n, %)	165 (43.0%)	122 (42.2%)	43 (45.3%)	292 (33.9%)	0.002	0.002	0.03
Living at home (n, %)	352 (91.7%)	62 (90.7%)	90 (94.7%)	756 (87.8%)	0.42	0.22	0.23
Prestroke mRS score (median, IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.28	0.20	0.13
Field SBP, mean (SD)	156.8 (±28.2)	155.8 (±27.4)	159.7 (±28.2)	155.3 (±26.6)	0.48	0.38	0.14
Field DBP, mean (SD)	86.9 (±-17.4)	86.0 (±17.2)	89.3 (±17.8)	87.3 (±17.6)	0.46	0.67	0.30
LKW to prehospital LAMS time (min, median (IQR)	22 (14–40)	24 (15–43)	20 (14–30)	24 (14–43)	0.19	0.18	0.20
Prehospital LAMS to ED-LAMS time (min, median (IQR)	32 (26–38)	32 (27–39)	30 (26–36)	33 (28–39)	0.008	0.002	0.001
Prehospital LAMS score					<0.0001	0.04	<0.0001
Median (IQR)	4 (3–5)	3 (3–5)	5 (4–5)	4 (3–5)			
Mean (SD)	3.6 (1.4)	3.6 (1.4)	4.7 (0/5)	3.6 (1.4)			
ED-LAMS score					<0.0001	<0.0001	<0.0001
Median (IQR)	1 (0–2)	1 (0–2)	0 (0–1)	4 (3–5)			
Mean (SD)	3.7 (1.5)	1.2 (1.1)	0.3 (0.5)	3.7 (1.5)			
ED NIHSS score median (IQR)	2 (0–5)	3 (1–6)	0 (0–2)	11 (5–18)	<0.0001	<0.0001	<0.0001
IV t-PA (n, %)	82 (21.4%)	68 (23.5%)	14 (14.7%)	366 (42.5%)	<0.0001	<0.0001	<0.0001
Endovascular treatment (n, %)	7 (1.8%)	4 (1.4%)	3 (3.2%)	45 (5.2%)	0.0088	0.67	0.73

ED NIHSS score = emergency department NIH Stroke Scale score; IV t-PA = IV tissue plasminogen activator; U-RNI = ultra-rapid neurological improvement; mRS = modified Rankin Scale; LKW to prehospital LAMS time = last known well to prehospital Los Angeles Motor Scale time; prehospital LAMS to ED-LAMS time = prehospital Los Angeles Motor Scale to emergency department Los Angeles Motor Scale time; mRS = modified Rankin Scale.

Table 2 Frequency of Outcomes for Patients With Acute Cerebral Ischemia With and Without Ultra-Early Rapid Neurologic Improvement

Outcomes	Any U-RNI, N = 384 (missing 6)	Moderate U-RNI, N = 289 (missing 5)	Dramatic U-RNI, N = 95 (missing 1)	No U-RNI, N = 861 (missing 9)	*p* Value
Excellent outcome at 90 d[a] (mRS score = 0–1) (N, %)	246/384 (64.0%)	178/289 (62.7%)	68/95 (72.3%)	302/861 (35.4%)	<0.0001
Dead by 90 d[a] (mRS score = 6) (N, %)	14/384 (3.6%)	13/289 (4.6%)	1/95 (1.1%)	140/861 (16.4%)	<0.0001
SICH (N, %)	6/384 (2.1%)	6/289 (2.1%)	0/95 (0.0%)	40/861(4.6%)	0.0133
Discharged home (N, %)	218/384 (56.8%)	155/289 (53.6%)	63/95 (66.3%)	260/861 (30.2%)	<0.0001
Discharged other than home	166/384 (43.2%)	134/289 (46.4%)	32/95 (33.7%)	601/861 (69.8%)	<0.0001
Acute rehab	47/384 (12.2%)	41/289 (14.1%)	6/65 (9.2%)	192/861 (22.3%)	
Another acute care hospital	73/384 (19.0%)	53/289 (18.3%)	20/65 (30.7%)	211/861(24.5%)	
Hospice	0/384 (0.0%)	0/289 (0.0%)	0/65 (0.0%)	12/861(1.4%)	
Other	7/384 (1.8)	7/289 (2.4%)	0/65 (0.0%)	11/861(1.3%)	
Relative or friend's home	9/384 (2.3%)	7/289 (2.4%)	2/65 (10.7%)	15/861 (1.7%)	
Skilled nursing facility	15/384 (3.9%)	12/289(4.1%)	3/65 (4.6%)	69/861(8.0%)	
Subacute rehab	10/384 (2.6%)	9/289 (3.1%)	1/65 (1.5%)	40/861(4.6%)	
Expired	5/384 (1.3%)	5/289 (1.7%)	0/65 (0.0%)	51/861 (5.9%)	
NIHSS at 24 h, mean (SD)	2.3 (1.4)	3.3 (5.7)	1.3 (4.1)	10 (10)	<0.0001
Final diagnosis TIA (tissue based) (N, %)	142 (47.4%)	84 (29%)	58 (61%)	80 (9%)	<0.0001
Final diagnosis TIA (time based) (N, %)	196 (51%)	126 (44%)	70 (74%)	112 (13%)	<0.0001
Postarrival neurologic deterioration (≥4 NIHSS score) (N, %)	22 (5.7%)	20 (7%)	2 (2%)	89 (10%)	0.01
Length of hospital stay (days) (median, IQR)	2.5 (2–3)	3 (2–4)	2 (1–4)	4 (2–6)	<0.0001
NIHSS at 90 d (median, IQR)	0 (0–4)	0 (0–4)	0 (0–2)	3 (1–18)	<0.0001

ED = emergency department; IQR = interquartile range; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; SICH = symptomatic intracranial hemorrhage; U-RNI = ultra-rapid neurologic improvement.
[a] Missing outcome data total 15 (no U-RNI = 9; moderate U-RNI = 5 and dramatic U-RNI = 1).

Patients with U-RNI had less severe initial neurologic deficits, less history of diabetes, atrial fibrillation, and coronary artery disease, while they more frequently reported history of alcohol use. Patients with U-RNI had improved early and 90-day outcomes, including 2–3-fold increased odds of excellent recovery at 90 days and a 3–10-fold increased odds of survival at 90 days. Nonetheless, adverse outcomes were not infrequent among patients with U-RNI, with nearly 1 in 4 patients showing dependency or death at 90 days. This was a prospective, multicenter investigation of rapid neurologic improvement in the prehospital and early ED course during the first minutes and hours after symptom onset in a broad, ambulance-transported, acute cerebral ischemia population using a validated quantitative stroke scale.

A recent study[16] using a qualitative instrument, reported the rate of prehospital clinical fluctuations in patients presenting with mild stroke symptoms and found that 36% of patients experience these fluctuations. Among those with fluctuations, 71% demonstrated only improvements, whereas 14% demonstrated fluctuations of both worsening and improvement.[16] However, the assessments used in this study were based on verbal reports by patients, family, or paramedics and are not quantitative and difficult to confirm.[16]

Our findings are consistent with and importantly extend prior studies. The preponderance of prior studies evaluated rapid improvement in stroke symptoms occurring later in disease course, between a first evaluation soon after ED arrival and a later in-hospital examination. These studies found a lower frequency of RNI than the present investigation, ranging from 5% to 24%.[1-3]

The current study's median time to first examination after LKW of 29.7 minutes is 1 hour earlier than the first examination time of 90 minutes in the analysis of the NINDS-t-PA Stroke Study.[3] The other studies did not report time of initial examination, but enrolled patients up to 4.5 hours and 6 hours after LKW so likely had even later first evaluations.[1,2] The current

Table 3 Outcomes Related to Moderate and Dramatic Ultra-Early Rapid Neurologic Improvement

Variable	OR	95% CI	*p* Value
Excellent recovery (mRS score 0–1) at 90 d			
Moderate U-RNI	2.71	1.97–3.74	0.0000
Dramatic U-RNI	3.78	2.19–6.54	0.0000
Age, per year	0.98	0.97–0.99	<0.0001
Prestroke mRS score 2 vs 0	0.02	0.01–0.07	0.0000
Prestroke mRS score 3–4 vs 0	0.00	0.00–0.00	0.9677
Serum glucose, per log unit	0.09	0.03–0.25	<0.0000
ASPECTS, per point	1.18	1.11–1.25	<0.0000
IV t-PA (yes/no)	0.47	0.36–0.63	<0.0000
Endovascular treatment (yes/no)	0.33	0.15–0.73	0.0065
C statistic 0.80; sensitivity (n = 548) 78.8%; specificity (n = 682) 65.5%; accuracy 72.2%			
Variable	**OR**	**95% CI**	***p* Value**
Death by 90 d			
Moderate U-RNI	0.27	0.15–0.50	<0.0000
Dramatic U-RNI	0.08	0.01–0.56	0.0113
Age, per year	1.07	1.05–1.09	<0.0000
Serum glucose, per log unit	30.5	7.94–117.4	<0.0000
ASPECTS, per point	0.82	0.76–0.87	<0.0000
Endovascular treatment (yes/no)	2.32	1.12–4.82	0.0237
C statistic 0.80; sensitivity (n = 154) 72.1%; specificity (n 1,076) 73.0%; accuracy 72.6%			
Variable	**OR**	**95% CI**	***p* Value**
Symptomatic intracranial hemorrhage by day 4			
Moderate U-RNI and dramatic U-RNI*	0.53	0.21–1.30	0.1625
ASPECTS, per point	0.85	0.77–0.95	0.0025
IV t-PA (yes/no)	2.64	1.36–5.12	0.0041
Diabetes (yes/no)	2.47	1.32–4.60	0.0045
log LKW to pre-LAMS (per log unit)	0.36	0.14–0.93	0.0343
C-statistic 0.78; sensitivity (n = 46) 84.8%; specificity (n = 1,184) 58.5%; accuracy 71.7%.			
Variable	**OR**	**95% CI**	***p* Value**
Discharge to home			
Moderate U-RNI	2.37	1.76–3.18	<0.0000
Dramatic U-RNI	3.54	2.18–5.73	<0.0000
Age, per year	0.96	0.95–0.97	0.0000
Log glucose, per log unit	0.15	0.06–0.40	0.0001
ASPECTS, per point	1.21	1.14–1.29	<0.0000
IV t-PA (yes/no)	0.58	0.44–0.77	<0.0000
Endovascular treatment (yes/no)	0.38	0.16–0.89	0.0263
C statistic 0.73; sensitivity (n = 474) 61.8; specificity (n = 756) 73.7%; accuracy 67.7%.			

OR = odds ratio; U-RNI = ultra-early rapid neurologic improvement; mRS = modified Rankin Scale; ASPECTS = Alberta Stroke Program Early CT Score; IV t-PA = IV tissue plasminogen activator; SICH = symptomatic intracranial hemorrhage; C statistic = concordance statistic = ROC area.

study, by analyzing assessments performed in the field, was able to capture an earlier part of stroke symptom course, when deficits are less stable and more subject to change.[17]

The current study of U-RNI complements a prior investigation in the FAST-MAG population of the frequency and outcomes of ultra-early neurologic deterioration in the prehospital and ED course. That study assessed serial Glasgow Coma Scale scores, which provides insight into worsening but not improvement as the Glasgow Coma Scale has a ceiling effect in ACI rendering it insensitive to improvement detection.[18]

By focusing on changes in the LAMS, a scale designed to be sensitive to ischemic stroke deficits, the current study was able to capture early neurologic improvements.[19,20] The systematic implementation of prehospital LAMS has demonstrated to be feasible with high adherence and useful to improve acute stroke triage decisions in clinical practice.[21]

Together, the studies indicate that patients with ACI are substantially more likely to improve (31%) than to worsen (7%) in the ultra-early period and that only 62% of patients have a stable initial course. This finding indicates that, in studies developing stroke severity scales for prehospital use, it is best to derive scale components and weights from prehospital rather than in-hospital examinations, as many patients look different when first encountered in the field than when subsequently encountered in the ED.

This study reinforces the finding of a low rate of early neurologic deficit progression in ACI, with the 7% rate measured in the current analysis of serial LAMS scores closely matching the 6% rate assessed with serial Glasgow Coma Scales scores in the prior FAST-MAG analysis.[18]

Among the patients with ACI transported by paramedics, 5 clinical variables were associated with U-RNI: less severe initial

neurologic deficits, less diabetes, less atrial fibrillation, less coronary artery disease, and more frequent current alcohol use. The association of U-RNI with the absence of comorbidities of diabetes, atrial fibrillation, and coronary artery disease likely reflects that body and brain prestroke robustness predisposes to early neurologic improvement. The association of U-RNI with less severe initial deficits likely arises because (1) patients with milder deficits typically have less clot burden as their occlusions are in smaller arteries, so the rate of spontaneous lysis is higher, and (2) patients with milder deficits typically have developed collaterals, so that the rate of re-establishment of adequate blood flow via collateral channels is higher. The association of current alcohol use with U-RNI is likely related to the known alcohol antiplatelet and fibrinolysis enhancing effects, diminishing clot propagation, and facilitating spontaneous clot lysis.[22,23] It is also possible that patients reporting current alcohol use had alcohol intoxication mimicking TIA; however, a clinical event adjudication committee reviewing all data in each patient determined that patients included in this analysis all had genuine TIA or ischemic stroke.

Among patients with ACI, U-RNI was associated with improved in-hospital and 90-day outcomes. In fact, one-half of patients with U-RNI fully resolved their neurologic deficits by 24 hours and had a final diagnosis of TIA, compared with a 13% rate of TIA among patients with no U-RNI.

The occurrence of moderate and dramatic U-RNI increased the odds of excellent recovery at 90 days and of survival to 90 days several-fold. However, unfavorable outcomes were not infrequent with U-RNI, with dependency or death at 90 days occurring in nearly one-quarter of U-RNI patients. This finding highlights a need for investigations to characterize the risk factors for, and mechanisms of, unfavorable long-term outcome despite the initial neurologic improvement. Treatment interventions to avert unfavorable outcome could then be intelligently applied. For prehospital system planning, the present study provides unique insight into the frequency of neurologic improvement occurring between paramedic evaluation in the field and ED arrival. Our study findings indicated that emergency medical service system planners may anticipate that approximately 1 in 3 patients with acute cerebral ischemia will experience a rapid improvement in stroke symptoms between the scene and ED arrival. This information may be useful for routing decisions and future prehospital interventions/research studies development.

This study has limitations. First, the analysis was confined to patients enrolled in a clinical trial. Although the FAST-MAG trial entry criteria were broad in age, stroke severity, and comorbidities, the study did exclude patients with prestroke disability, systolic blood pressure greater than 220 mm Hg, bilateral weakness, and other uncommon features of ACI.

Specifically, coma was an exclusion criterion—it is possible that strokes due to basilar thrombosis presenting with coma were not included. Such patients may have different frequencies of U-RNI. Stroke mimics within the patients with rapid neurologic improvement cannot completely ruled out. The interval from prehospital to ED-LAMS evaluation was somewhat extended, reflecting study nurse travel time to the ED.

The present study used change in LAMS scores to identify neurologic improvement. Because the LAMS focuses on motor deficits, it will not capture change in language, visual, sensory, and other domains. However, motor deficits are present in 80%–90% of all strokes and their evolution most often parallels that of deficits in other domains.[24] Studies of in-hospital neurologic improvement among patients with ACI have most often focused on improvements in the NIHSS score, but assessments using this scale are too time consuming for routine use in the field by paramedics. The LAMS is a validated stroke severity assessment tool with good concurrent, discriminant, and predictive validity.[7-12] LAMS scores correlate closely with full NIHSS scores and predict 90-day outcome comparably to the NIHSS.[7] The LAMS performs comparably or better than other prehospital stroke severity instruments in identifying patients with ACI with large vessel occlusions.[8,19,20] It is possible that those patients with dramatic U-RNI who started with a LAMS of 4 or 5 were harboring a large vessel occlusion that spontaneously lysed within the first 50–60 minutes (time from last time know well to prehospital LAMS plus from prehospital to ED-LAMS).

Ultra-early rapid neurologic improvement occurs in nearly 1 in 3 ambulance-transported patients with acute cerebral ischemia and is associated with substantially increased excellent recovery and decreased mortality at 90 days. Accounting for U-RNI may be useful for routing decisions and future prehospital interventions.

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Disclosure

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Continued

Appendix (continued)

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