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Time to presentation is associated with clinical outcome in hemispheric stroke patients deemed ineligible for recanalization therapy

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Abstract

Background—Delayed thrombolysis adversely impacts functional outcome after stroke. Therefore, great efforts are undertaken to reduce delay in patient presentation and initiate treatment as quickly as possible. However, little is known regarding the impact of time to presentation (TTP) on outcome in patients that are ineligible for acute stroke therapy. Thus, we sought to determine whether the TTP is associated with the 90-day outcome irrespective of eligibility for acute recanalization therapy.

Methods—We retrospectively analyzed 258 consecutive acute ischemic stroke patients evaluated between January 2013 and February 2014. Multivariable logistic regression was used to determine whether a greater TTP is independently associated with a poor 90-day outcome as defined as a modified Rankin scale (mRS) score of 3–6.

Results—In unadjusted analyses the TTP was inversely correlated with transfer from an acute facility ($r=-.126$, $P=0.043$), cardioembolic stroke etiology ($r=-.146$, $P=0.019$), and acute

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Author contributions

Yunis Mayasi	Data acquisition, interpretation of data, and drafting the article
Johanna Helenius	Data acquisition, critical revision of the manuscript for important intellectual content
Richard P. Goddeau, Jr.	Critical revision of the manuscript for important intellectual content
Majaz Moonis	Critical revision of the manuscript for important intellectual content
Nils Henninger	Study concept and design, data acquisition, statistical analysis, interpretation of data, and drafting the article

Disclosures

None.

recanalization therapy ($r=-.412$, $P<0.001$). Conversely, a longer TTP correlated with a worse 90-day mRS ($r=.127$, $P=0.045$). After adjustment, the TTP ($P=0.019$), age ($P<0.001$), female sex ($P=0.001$), National Institute of Health Stroke Scale score ($P<0.001$), pre-admission mRS ($P=0.001$), atrial fibrillation ($P<0.001$), and infarct volume ($P<0.001$) were independently associated with a poor 90-day outcome. Importantly, a longer TTP (OR 1.016; 95%-CI 1.001 to 1.032; $P=0.036$) remained independently associated with the 90-day outcome when we restricted analyses to patients ineligible for acute intravenous and endovascular recanalization therapies.

Conclusions—Each hour delay in the TTP decreased chances for good outcome by approximately 2% independent of patient eligibility for acute recanalization therapies.

Keywords

cerebral infarction; modified Rankin Scale; time to presentation; tPA; endovascular intervention

Introduction

Ischemic stroke remains one of the leading causes of morbidity and mortality worldwide;¹ one in six individuals is predicted to suffer a stroke in their lifetime.² The advent of intravenous (i.v.) thrombolysis with recombinant tissue-type plasminogen activator (rtPA) as well as recent breakthroughs in endovascular stroke therapy (EST) have revolutionized acute stroke care.^{3–6} Nevertheless, a major prevailing issue relates to the fact that only a minority of patients is eligible to receive these treatments.^{7,8}

The causes for this are multifold but delayed presentation of patients represents a main reason why patients are ineligible for emergent i.v. thrombolysis or EST. Furthermore, later initiation of thrombolytic therapy is associated with reduced treatment efficacy.⁵ Accordingly, substantial efforts have been made to improve patient presentation early to the hospital as well as to decrease in-hospital delays of patient evaluation to increase patient eligibility for acute intervention and overall increased chance for a good outcome.^{4–6,9}

However, there is a paucity of data whether the time to presentation (TTP) relates to post-stroke outcome irrespective of acute therapy; to our knowledge only a single study has investigated this issue more than 2 decades ago.¹⁰ Thus, we sought to determine whether a longer TTP in patients deemed ineligible for i.v. thrombolysis or EST is associated with the 90-day functional status after stroke in a contemporary stroke patient cohort. We hypothesized that a longer TTP is an independent risk factor for a poor 90-day outcome irrespective of patient eligibility for acute therapy.

Materials and Methods

Study cohort

We retrospectively analyzed patients prospectively included in our local stroke registry between January 2013 and February 2014. The investigation was approved by our Institutional Review Board and Health Insurance Portability and Accountability Act waiver of consent was granted. We adhere to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.¹¹

We included patients presenting to a university-affiliated emergency department with an acute hemispheric ischemic stroke. We only included patients with available brain MRI to allow for reliably quantifying the infarct volume. Furthermore, we excluded patients with infratentorial infarct location from the present analyses because of their frequent delay to presentation¹² as well as the fact that outcome predicting variables differ from supratentorial strokes.^{13–15} Included patients have been described as part of a previously published studies.^{16,17} All patients were evaluated by stroke-trained physicians. Patient demographics, laboratory data, co-morbidities, pre-admission medications, and stroke etiology (using the Trial of Org 10 172 in Acute Stroke Treatment [TOAST] classification^{16–18}), after completion of diagnostic evaluation, were collected on all patients. In addition, we collected information whether patients presented from home, acute, or chronic care facilities. The National Institute of Health Stroke Scale (NIHSS) score at presentation was determined by certified members of the stroke team. All patients were treated in accordance to the American Heart Association secondary stroke prevention guidelines, which includes early implementation of statin and antithrombotic therapy as appropriate.¹⁹

We defined the TTP as the time from documented symptom onset or time from last known well to the time of presentation in the emergency department. The pre-admission and 90-day modified Rankin Scale (mRS) score was assessed by a certified stroke-trained physician or stroke study nurse, in a face to face interview or by a structured phone interview.^{16,20} The 90-day outcome was dichotomized to good (mRS 0–2) vs. poor (mRS 3–6).

Definition of acute treatment eligibility

Ineligibility for treatment with i.v. rtPA was determined according to current guidelines.²¹ Patient eligibility for EST at our institution is in general accord with the inclusion criteria of the recent positive endovascular stroke trials.^{3,22,23} In brief, patients were considered for EST if they presented within 8 hours of symptoms onset, had a documented large arterial occlusion (distal internal carotid artery, middle cerebral artery [M1/M2], or anterior cerebral artery [A1/A2]), and a small ischemic core as determined by either diffusion-weighted imaging (DWI)-lesion <100 mL or an Alberta Stroke Program Early CT score (ASPECTS) >6 on admission head CT, and had no other documented absolute contraindication for treatment, including hypersensitivity to nickel-titanium, stenosis and/or previous stenting proximal to the thrombus, and evidence of dissection in addition to patient refusal.^{3,22,23}

Risk factor definitions

We determined the presence of hypertension (use of antihypertensive medications, or systolic blood pressure of ≥ 140 mm Hg or diastolic blood pressure of ≥ 90 mm Hg on two separate occasions after the first several days of hospitalization¹⁹), hypercholesterolemia (use of lipid-lowering agents, or fasting blood total cholesterol level of ≥ 200 mg/dl or low density lipoprotein cholesterol of ≥ 130 mg/dl) and diabetes mellitus (defined according to the National Diabetes Data Group and World Health Organization²⁴). Cardiac studies included transthoracic echocardiography or transesophageal echocardiography, electrocardiography, in-house continuous event monitoring, and 30-day event monitoring in patients with suspected paroxysmal atrial fibrillation.

Neuroimaging protocol

Brain MRI included T1-, T2-, and fluid attenuated inversion recovery (FLAIR)-sequences as well as DWI obtained on a 1.5 Tesla scanner (GE Signa; GE Medical Systems, Milwaukee, WI) as previously detailed.¹⁶

Statistics

Unless otherwise stated, continuous variables are reported as mean $\pm$ s.d. or as median (interquartile range [IQR]). Categorical variables are reported as proportions. Normality of data was examined using Shapiro-Wilk test. Between-group comparisons for continuous variables were made with Mann-Whitney U test. Categorical variables were compared using the χ^2 -test or Fisher's Exact test. Spearman rank correlation was used to determine the strength of association between the continuous variables and the TTP. Receiver operating characteristic (ROC) curves were plotted to determine the optimal TTP predicting a good 90-day outcome.

The primary goal of our study was to determine whether the TTP was associated with the 90-day outcome independent of acute recanalization therapy (i.v. rtPA or EST). To this end we first constructed a multivariable logistic regression model with backward elimination adjusting for acute recanalization therapy as well as factors that have been associated with the outcome and stroke severity, namely: age, sex, admission NIHSS, pre-admission mRS, infarct volume, history of stroke/transient ischemic attack, hypertension, atrial fibrillation, random glucose as well as use of anticoagulants, antiplatelets, and HMG-CoA reductase inhibitors. Then, we reanalyzed our data restricted to patients that were deemed ineligible for acute recanalization therapy with i.v. rtPA or EST (n=187) to avoid confounding by unmeasured factors that are unique to treatment eligible patients.

Collinearity diagnostics were performed (and its presence rejected) for all multivariable regression models. Two-sided significance tests were used throughout and a two-sided $P<0.05$ was considered statistically significant. All statistical analyses were performed using IBM® SPSS® Statistics 22 (IBM®-Armonk, NY).

Results

Study participants

In brief, during the study period, 434 patients with a clinical diagnosis of ischemic stroke or transient ischemic attack had a brain MRI allowing for reliable determination of infarct presence and extent. We excluded patients that had no ischemic infarct on MRI (n=61), infratentorial infarct location (n=55), patients with a stroke during hospitalization (n=6), patients transferred from a different hospital without documented time of presentation (n=12), undetermined time of symptom onset (i.e., incidental diagnosis of ischemic stroke on neuroimaging; n=26), clerical errors (e.g., documented presentation prior to symptom onset; n=3) or because patients were lost to follow up (n=13); leaving 258 patients for analysis. Data was complete in included patients for all investigated variables.

Clinical characteristics

Baseline characteristics of included patients as stratified by the 90-day outcome are summarized in Table 1. Compared to patients with a good outcome, patients with a poor 90-day outcome presented later to the emergency room ($P=0.019$), had larger infarct volumes ($P<0.001$), greater admission NIHSS ($P<0.001$), worse pre-admission mRS ($P<0.001$), were older ($P<0.001$), more frequently female ($P=0.001$), had more frequently a history of atrial fibrillation ($P<0.001$), hypertension ($P=0.011$), coronary artery disease ($P=0.037$), and congestive heart failure ($P=0.019$) as well as were more likely to have a cardioembolic stroke ($P=0.043$) and less likely to have a small vessel disease related stroke ($P=0.012$).

Factors correlated with the TTP

In the entire cohort, the median TTP was 3.8 hours (IQR 10.8 hours). To determine factors associated with the TTP we first conducted correlative analyses. Overall, there was an inverse correlation between the TTP with transfer from an acute facility ($r=-.126$, $P=0.043$), cardioembolic stroke etiology ($r=-.146$, $P=0.019$), and any acute recanalization therapy ($r=-.412$, $P<0.001$). Conversely, a longer TTP correlated with a worse 90-day mRS ($r=.127$, $P=0.045$). The correlation with presentation from home approached significance ($r=.119$, $P=0.057$). All other baseline characteristics did not significantly correlate with the TTP ($P>0.05$ each, not shown).

ROC curve analysis of the TTP discriminating good vs. poor outcome

For the entire cohort, TTP ROC curve analyses did not allow for reliably separating a good from a poor outcome (area under the ROC curve, 0.598; 95% confidence interval [CI] 0.519–0.676; $P=0.019$). Results were similar when analyses were conducted separately for patients eligible (area under the ROC curve, 0.476; 95%-CI 0.305–0.647; $P=0.778$) or ineligible for acute therapy (area under the ROC curve, 0.599; 95%-CI 0.511–0.686; $P=0.038$). Given these results we did not attempt to calculate a TTP threshold best discriminating a good from poor outcome in our cohort.

Comparison of patients eligible vs. ineligible for acute therapy

Patients that were ineligible ($n=187$; 72%) for acute recanalization therapy presented significantly later (5.4 [IQR 14.1] hours vs. 1.2 [IQR 2.3] hours, $P<0.001$), and had a lower admission NIHSS (6 ± 7 vs. 10 ± 6 , $P<0.001$), lower random glucose level (133 ± 64 vs. 135 ± 44 mg/dL, $P=0.044$), less frequently a cardioembolic stroke etiology (37% vs. 54%, $P=0.017$), and more frequently a small vessel disease related stroke etiology (12% vs. 3%, $P=0.030$) than patients that were eligible for treatment ($n=71$). All other baseline characteristics were not significantly different between patients eligible vs. ineligible for i.v. thrombolysis or EST ($P>0.05$ each, not shown).

Independent association of the TTP with the 90-day outcome

Table 3 summarizes the results from the multivariable logistic regression analyses. In essence, we found that a longer TTP ($P=0.004$) was associated with a poor 90-day outcome independent of age ($P<0.001$), admission NIHSS ($P<0.001$), infarct volume ($P=0.006$), and random blood glucose ($P=0.04$). Removal of two patients with two extreme TTPs (183 and

313 hours) did not meaningfully change the association between the TTP and 90-day outcome (not shown).

Reanalyzing our data restricted to patients that were ineligible for acute i.v. thrombolysis or EST (n=187) confirmed the independent association of a longer TTP with a poor 90-day outcome ($P=0.036$, Table 3). Conversely, in the relatively small subgroup of eligible patients (n=71) only atrial fibrillation ($p=0.033$), age ($p=0.009$, per decade), random blood glucose ($p=0.043$), and infarct volume ($p=0.015$) but not the TTP ($p>0.2$) were associated with the 90-day outcome (not shown). Lastly, in analyses restricted to patients excluded solely for the fact that they presented outside a therapeutic window the TTP ($p=0.046$), admission NIHSS ($p=0.001$), age ($p=0.030$, per decade), and pre-admission mRS ($p=0.026$) were independently associated with the 90-day outcome.

Discussion

The most important finding of our study was that the TTP was independently associated with a poor 90-day functional status after stroke. Importantly, this association was independent of acute recanalization therapy (i.v. rtPA and EST). This is an important finding because current efforts to reduce the TTP mainly focus on increasing patient eligibility for acute treatment as well as treatment efficacy; however, only a minority of stroke patients is eligible for these therapies.^{5,8}

Similar to observations in patients treated with i.v. thrombolysis we found that the TTP is a critical determinant of the post-stroke outcome.^{4,6} However, our data indicate that a longer TTP represents an important risk factor for a poor outcome among ischemic stroke patients who are not eligible for acute recanalization therapies—a finding that applies to the vast majority of acute stroke patients. Similar observations have been made in a study conducted in the mid-90s.¹⁰ However, this study did not adjust for important predictors of the post-stroke outcome such as comorbidities, infarct volume, and concurrent medical therapy and long-term outcomes were not assessed.¹⁰ More importantly, since then the introduction of novel secondary stroke prevention measures as well as the implementation of evidence based stroke therapy guidelines and dedicated stroke units have changed stroke care substantially, resulting in overall better patient outcomes.^{10,25–27} Thus, our results from a contemporary acute stroke cohort highlight the importance of timely evaluation of stroke patients—irrespective of presumed eligibility for recanalization therapies. The timeliness of better understanding this association is highlighted by concerns that the current focus of expedited identification and evaluation of stroke patients to enhance acute interventions, increasingly allocates finite resources to benefit only a select minority of patients.²⁸ Accordingly, our observation suggest that approaches seeking to hasten patient evaluation in the hyperacute setting may ultimately benefit a much larger proportion of patients than only those found eligible for acute stroke therapy.

Notably, when we performed an analysis restricted to patients that underwent acute recanalization therapy, the TTP was not associated with the 90-day outcome. However, this analysis was underpowered to detect such an association. Further, in this subgroup a significant proportion of patients had received EST. EST has been shown to benefit patients

presenting beyond the established time window thereby biasing the results towards the null hypothesis.²⁹

Multiple studies have shown that early patient presentation and vessel recanalization is a critical determinant of treatment efficacy and outcome.^{5,10,30,31} However, it is unclear why a longer TTP is an important risk factor for a poor functional outcome in patients that are not treated with recanalizing therapies. Possible reasons may relate to more rapid identification of the underlying etiology and implementation of appropriate evidence based secondary stroke prevention measures.³² Additionally, early initiation of preventative measures for stroke-related complications such as deep vein thrombosis or aspiration pneumonia or rehabilitative efforts may contribute to improved functional outcomes.^{33–36} Identifying the specific factors in future studies will be important to improve patient outcomes.

Strengths of our study relate to inclusion of consecutive patients with imaging confirmed ischemic stroke that were evaluated by clinicians certified in NIHSS and mRS, in addition to the rigorous adjustment for important outcome predicting variables. Limitations relate to its retrospective research question. Thus, while we demonstrate a strong association of the TTP with the 90-day outcome our research design does not allow us to establish causality. Accordingly, results should only be considered hypothesis generating. Further, we included patients in whom symptom onset was estimated by the time from last known well. However, the number of patients with such defined symptom onset was similar in patients with a good vs. poor outcome assuaging concerns that this introduced a significant bias. Furthermore, this approach represents clinical practice and thus allows for better generalization of our results. Exclusion of patients without brain MRI may have introduced a bias. For example, MRI may not be obtained in the presence of contraindications (such as MRI-incompatible cardiac pacemakers and defibrillators) or severe strokes when MRI is not expected to change clinical management. Hence, excluded patients may have different outcomes from included patients because of differing vascular risk factor profiles as well as stroke severity and etiology.¹⁷ Although this may affect the generalizability of our results our approach allowed for rigorous adjustment for the infarct volume, which is one of the most important predictors of the post-stroke outcome.³⁷ Lastly, since we excluded patients with infratentorial strokes it remains to be shown whether our results also apply to this population.

Conclusions

Delayed TTP after ischemic stroke is associated with a poor 90-day outcome independent of patient ineligibility for acute revascularization therapy with i.v. thrombolysis or EST. This information is important to educate patients at risk for stroke and their care-givers as well as medical staff caring for acute stroke patients.

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Table 1

Baseline characteristics (unadjusted) of the studied patient population as stratified by 90-day outcome

Characteristics	All patients (n=258)	Good outcome (n=193)	Poor outcome (n=65)	P-value
Age, years	69 (21)	67 (18)	82 (22)	<0.001
Female sex	114 (44%)	74 (38%)	40 (62%)	0.001
Admission NIHSS	8 (10)	6 (7)	14 (10)	<0.001
Admission glucose, mg/dL	119 (44)	116 (40)	132 (63)	0.010
Admission creatinine, mg/dL	0.97 (0.41)	0.95 (0.38)	1.03 (0.49)	0.187
Pre-admission mRS	0 (1)	0 (0)	1 (2)	<0.001
Time to presentation, hours	3.8 (10.8)	3.5 (9.5)	4.7 (14.8)	0.019
Symptom onset defined by LKW time	117 (45%)	85 (44%)	32 (49.2%)	0.475
Presentation from home	191 (74%)	144 (75%)	47 (72%)	0.745
Presentation from an acute care facility	61 (24%)	46 (24%)	15 (23%)	1.000
Presentation from a chronic care facility	6 (2%)	3 (2%)	3 (5%)	0.170
Pre-admission medications				
Statin	109 (42%)	80 (42%)	29 (45%)	0.829
Antihypertensive	175 (68%)	126 (65%)	49 (75%)	0.167
Antiglycemic	52 (20%)	40 (21%)	12 (19%)	0.858
Antiplatelets	130 (50%)	92 (48%)	38 (59%)	0.152
Oral anticoagulant	18 (7%)	10 (5%)	8 (12%)	0.086
Pre-existing risk factors				
Hypertension	196 (76%)	139 (72%)	57 (88%)	0.011
Dyslipidemia	136 (53%)	99 (51%)	37 (57%)	0.474
Diabetes	75 (29%)	55 (29%)	20 (31%)	0.753
Prior stroke or transient ischemic attack	51 (20%)	36 (19%)	15 (23%)	0.473
Atrial fibrillation	50 (20%)	26 (14%)	24 (37%)	<0.001
Coronary artery disease	55 (21%)	35 (18%)	20 (31%)	0.037
Congestive heart failure	21 (8%)	11 (6%)	10 (15%)	0.019
Stroke subtype				
Large-artery atherosclerosis	69 (27%)	55 (29%)	14 (22%)	0.332
Cardioembolic	107 (42%)	73 (38%)	34 (52%)	0.043
Small vessel disease	24 (9%)	23 (12%)	1 (2%)	0.012
Stroke of undetermined cause	43 (17%)	29 (15%)	14 (22%)	0.249
Stroke of other determined cause	15 (6%)	13 (7%)	2 (3%)	0.369
Infarct properties				
Infarct volume, mL	4 (22)	13.4 (15)	24 (67)	<0.001
Left hemispheric infarction	147 (57%)	113 (59%)	34 (52%)	0.389
Right hemispheric infarction	85 (33%)	65 (34%)	20 (31%)	0.761
Bilateral infarction	26 (10%)	15 (8%)	11 (17%)	0.054
Eligible for acute intervention	71 (28%)	57 (30%)	14 (22%)	0.261
Intravenous thrombolysis*	59 (23%)	48 (25%)	11 (17%)	0.233

Characteristics	All patients (n=258)	Good outcome (n=193)	Poor outcome (n=65)	P-value
Endovascular stroke therapy	18 (7%)	14 (7%)	4 (6%)	1.000

Data are n (%) or median (interquartile range); LKW, last known well; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

* With our without endovascular stroke therapy.

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Table 2

Ineligibility criteria for acute stroke therapy in the entire cohort as stratified by 90-day outcome

Characteristics	All patients (n=258)	Good outcome (n=193)	Poor outcome (n=65)	P-value
Outside a therapeutic window [*]	113 (44%)	72 (37%)	41 (63%)	<0.001
Symptom severity too mild	49 (19%)	46 (24%)	3 (5%)	<0.001
Laboratory contraindications	5 (2%)	3 (2%)	2 (3%)	0.602
Miscellaneous [†]	20 (8%)	15 (8%)	5 (8%)	1.000

^{*} 3 to 4.5 hours for i.v. thrombolysis; 8 hours for EST.

[†] Includes, active bleeding (n=6), history of intracerebral hemorrhage (n=1), concurrent head trauma (n=2), uncontrolled hypertension (n=1), patient/family refusal (n=1), early signs of ischemia in more than 1/3rd of the middle cerebral artery territory (n=2), use of direct thrombin/factor Xa inhibitors (n=3), seizure at onset and uncertain stroke diagnosis (n=1), symptom resolution prior to rtPA bolus (n=3).

Table 3

Multivariable logistic regression analyses of factors independently associated with the 90-day outcome

Independent variable	Coefficient (95% CI)	P-value
Entire cohort (n=258)		
Time to presentation (per hour)	1.023 (1.007 to 1.039)	0.004
Admission NIHSS (per point)	1.131 (1.061 to 1.205)	<0.001
Random blood glucose (per dL)	1.006 (1.001 to 1.011)	0.040
Age (per decade)	1.872 (1.334 to 2.626)	<0.001
Atrial fibrillation	2.204 (0.928 to 5.235)	0.073
Infarct volume (per mL)	1.016 (1.004 to 1.027)	0.006
Pre-admission mRS	1.571 (1.101 to 2.241)	0.013
Patients ineligible for acute intervention (n=187)		
Time to presentation (per hour)	1.016 (1.001 to 1.032)	0.036
Admission NIHSS (per point)	1.249 (1.159 to 1.347)	<0.001
Age (per decade)	1.496 (1.061 to 2.111)	0.022
Pre-admission mRS	1.771 (1.172 to 2.677)	0.007

For analysis conducted on the entire cohort, sex, acute intervention, history of stroke/transient ischemic attack, coronary artery disease, and hypertension, as well as use of anticoagulants, antiplatelets, and HMG-CoA reductase inhibitor were not retained in the final model (Goodness-of-fit statistics: $\chi^2=8.068$, $p=0.427$). For analysis restricted to patients not eligible for acute intervention (either intravenous thrombolysis or endovascular stroke therapy), sex, history of stroke/transient ischemic attack, coronary artery disease, atrial fibrillation and hypertension, random glucose, infarct volume as well as use of anticoagulants, antiplatelets, and HMG-CoA reductase inhibitors were not retained in the final model (Goodness-of-fit statistics: $\chi^2=13.432$, $p=0.098$).