Novel Definition of Stroke "Good Responders" Predicts 90-Day Outcome after Thrombolysis

Alyssa E. Bautista, MD, Dawn M. Meyer, PhD, FNP-C, FAHA, and Brett C. Meyer, MD

Introduction: Identifying predictors of good response in thrombolytic-treated stroke is important to clinical care, resource allocation, and research design. We developed a simple, novel measure of "Good Responders" to assess if 2 short-term variables could predict 90-day outcomes after thrombolysis in stroke. *Methods:* Intravenous thrombolysis-treated stroke cases from June 2004 to June 2018 were analyzed from a stroke registry. Intraarterial treatment cases were excluded. Good responders (GR++) were defined as those with length of stay less than or equal to 3 days and discharge to home. Poor responders (GR--) had length of stay more than 3 days and discharge other than home. Mixed responders (GR+/-) composed the remainder. Baseline characteristics and predictors of 90-day outcome were assessed. *Results:* Of 261 patients, there were 101(38.7%) GR++, 67(25.7%) GR--, and 93(35.6%) GR+/-. For GR++ versus GR-- versus GR+/-, there were differences in mean age (62.7, 71.2, 69.2; $P = .0016$), and baseline modified Rankin score (mRS) 0-2 (%: 94.9, 74.6, 84.8; $P = .008$). Younger age, male sex, lower values for systolic BP, glucose, and baseline mRS were associated with good responders. Older age, atrial fibrillation, symptomatic intracerebral hemorrhage, and baseline mRS greater than 2 were associated with poor responders. At 90 days, mortality was reduced in GR++ versus GR-- versus GR+/- (%alive: 92.6, 72, 86; $P = .04$), and mRS(0-2) (%: 36.8, 0, 11.8; $P < .001$). *Conclusions:* Good responders to thrombolysis are younger and have better baseline functional status. Our novel definition of "Good Responders", using 2 early variables of home disposition and short length of stay, may help predict 90-day post-thrombolytic outcome. Future work should focus on validating this definition.

Key Words: Ischemic stroke—tissue plasminogen activator—outcomes—predictor

Introduction

Stroke is a leading cause of mortality and disability worldwide,[1,2] and a major source of economic burden.[3] An estimated $65 billion is lost to stroke in the United States, with two thirds accounted by direct costs (including acute and long term care), and the remainder third accounted by indirect costs that include lost productivity.[4]

The use of intravenous recombinant tissue plasminogen activator (rt-PA) since its approval in 1996, has become pivotal in reducing disability in stroke. About two thirds of eligible patients receive IV thrombolysis in the United States, with the rate nearly doubling over time.[5] The time it takes to improve after rt-PA varies among individuals, but certain variables have been correlated with good outcomes. Variables correlating with early improvement are not well elucidated, but studies have found an association between early neurologic improvement within 24 hours and favorable outcome at 3 months.[6-8] Even so, a proportion of patients still fail to demonstrate early recovery after thrombolysis.[8] In these studies, the National Institute of Health Stroke Scale (NIHSS) was the sole measure of clinical improvement, plotted against differing time

From the University of California, San Diego Stroke Center, San Diego, California.

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Address correspondence to Alyssa Bautista, MD, University of California, San Diego Stroke Center, 200 W. Arbor Drive, MC 8466, San Diego, CA 92103. E-mail: alyssabautista@gmail.com.

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frames. While unquestionably useful, utilizing the NIHSS poses some limitations,[9] cautious interpretation, and requires training and certification.

Identifying who will recover early from thrombolysis, and if early recovery will correlate with long term outcome, is still unknown. In order to eliminate NIHSS measurements and expand outcome measures to include patients that do not necessarily improve early within 24 hours, but improve nonetheless during hospitalization, we hypothesized that variables available early in the hospitalization of rt-PA patients may aide in longer term outcome prediction. We assessed if 2 clinically chosen variables (hospital length of stay [LOS] of 3 days or less, and discharge destination of home) could pragmatically predict 90-day outcome among rt-PA treated stroke patients.

Methods

We conducted a retrospective analysis of prospectively collected data from a database of consecutive acute stroke code patients seen from June 2004 to June 2018 at 1 of our facilities. Cases were included if they received IV rt-PA and had a final diagnosis of acute ischemic stroke. We excluded cases that underwent intra-arterial treatment to avoid confounding.

Patients were grouped based on 2 short-term variables (hospital LOS and discharge destination) after receiving rt-PA. "Good Responder" to rt-PA (GR++) category was defined as having 2+ variables (LOS ≤3 days AND discharge destination to home). "Poor Responder" (GR- -) category was defined as having 2- variables (LOS >3 days AND discharge destination to location other than to home). The "Mixed Responder" (GR+/-) category made up the remainder, both (LOS ≤ 3 days and discharge destination to location other than to home) and (LOS > 3 days and discharge destination to home) (Fig 1). Mortality and functional outcome at 90 days were compared. Favorable functional outcome was measured using the dichotomized modified Rankin scale score mRS(0-2).

All *P* values in continuous demographics tables (age, blood pressure, and glucose) were computed using ANOVA test and *P* values in categorical tables (gender, ethnicity, race, presence of coronary artery disease, diabetes mellitus, hypertension, atrial fibrillation, symptomatic intracerebral hemorrhage (ICH), smoking status, drinking status, and baseline mRS score) were computed using Fisher's Exact or Chi-squared where appropriate. Correlation coefficient for variables associated with good responders and poor responders were analyzed using Spearman *P* value. Variables for predictors of 90-day outcome were assessed using Pairwise Wilcox test and Fisher's test. For the adjusted odds ratios, data was adjusted for baseline NIHSS, age, baseline glucose, and smoking status. Further analysis to determine each contribution of LOS and discharge home to 90-day outcome was done with Spearman's rho (r^2). A *P* value of less than .05 was considered significant.

Results

A total of 261 patients met inclusion criteria and were included in our analysis. The subjects were stratified according to LOS and discharge destination: 101 (38.7%) were GR++, while 67 (25.7%) were GR- -, and 93 (35.6%) were GR+/-. Table 1 reports baseline characteristics according to the 3 groups. Among GR++ and GR+/- and

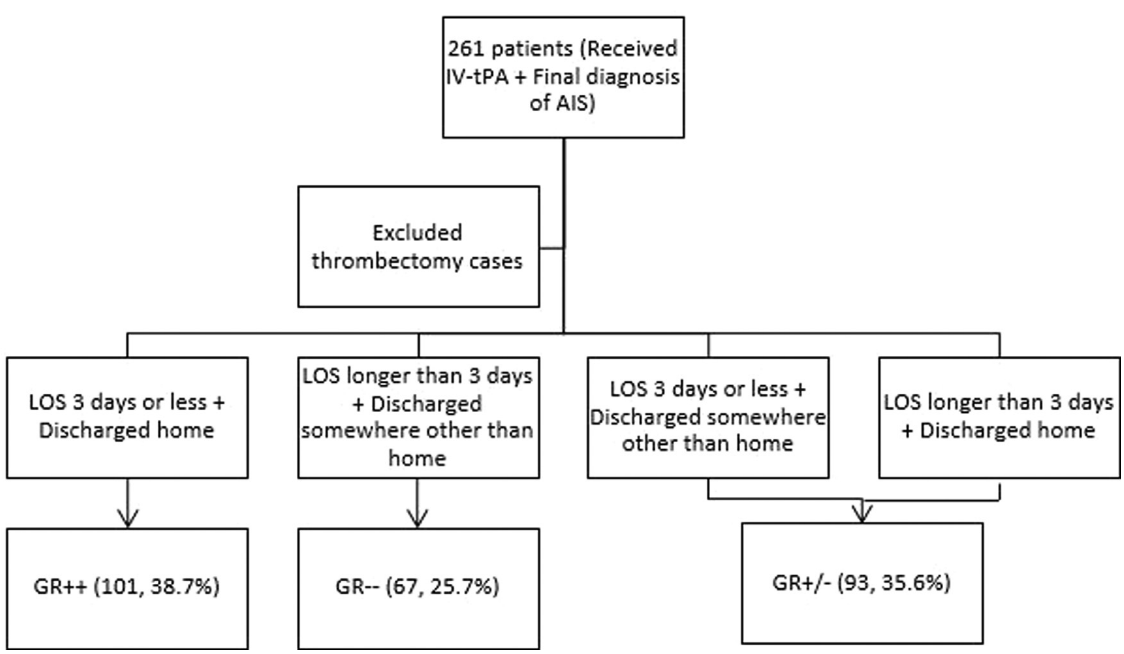

Figure 1. *Study profile.*

Table 1. *Baseline characteristics among good (GR++) versus mixed (GR+/-) versus poor (GR- -) responders to rt-PA*

	GR++ (n = 101)	GR+/- (n = 93)	GR- - (n = 67)	*P* Value
Age, mean	62.7	69.2	71.2	.002
Male	67 (66.3)	47 (50.3)	36 (53.7)	.06
Ethnicity				.54
Hispanic	21 (20.8)	19 (20.4)	13 (19.4)	
Not Hispanic	53 (79.1)	72 (77.4)	53 (79.1)	
Not reported	0	2 (2.1)	1 (1.5)	
Race				.11
White	56 (56)*	54 (58.7)*	43 (65.2)*	
Blacks	35 (35)*	30 (32.6)*	15 (22.7)*	
Native/Pacific islander	8 (8.0)*	2 (2.2)*	5 (7.6)*	
Asian	1 (1.0)*	6 (6.5)*	3 (4.5)*	
Medical history				
Hypertension	62 (61.4)	58 (62.4)	46 (68.7)	.61
Diabetes mellitus	18 (18.0)*	19 (20.4)	17 (25.4)	.51
Coronary artery disease	23 (22.8)	15 (16.1)	17 (25.8)*	
Atrial fibrillation	19 (19.0)*	21 (22.8)*	22 (32.8)	.12
Current smoker	12 (11.9)	16 (17.2)	7 (10.4)	.41
Current drinker	21 (20.8)	14 (15.1)	7 (10.4)	.21
Baseline mRS 0-2	94 (94.9)‡	78 (84.8)*	47 (74.6)†	.008
Intravenous thrombolysis				
Systolic blood pressure*, mean	145	152	151	.08
Glucose*, mean	129	130	133	.86
Symptomatic ICH	2 (2.0)	5 (5.4)	7 (10.4)	.06

Abbreviations: ICH, intracerebral hemorrhage; mRS, modified Rankin scale; rt-PA, recombinant tissue plasminogen activator.
Values expressed as no.(%) unless otherwise indicated.
*One missing value.
†Two missing values.
‡Four missing values.

GR- -, there were significant differences in mean age (62.7, 71.2, 69.2; *P* = .002), and baseline mRS score 0 to 2 (94.9%, 74.6%, 84.8%; *P* = .008).

Lower values for age, systolic BP, glucose, male sex, and baseline mRS were associated with "good responders" to rt-PA. Older age, presence of atrial fibrillation, symptomatic ICH, and baseline mRS greater than 2 were associated with "poor responders" to rt-PA.

Table 2 shows the 90-day outcomes among the 3 groups. Functional outcome at 90 days after rt-PA was favorable in GR++ compared to GR - - and GR+/- (36.8%, 0%, 11.8%; *P* < .001) (Fig 2). Mortality at 90 days after rt-PA was also significantly different among the groups; 92.6% of GR++ was alive at 90 days, compared to 72% for GR- -, and 86% for GR+/- (*P* = .04) (Fig 3). Interaction was similar between the 2 variables used; LOS accounted for 47.4% (*P* = 4.67) and discharge home accounted for 49.7% (*P* = 1.49) of 90-day outcome.

Discussion

Since the approval of IV rt-PA for stroke, clinicians and researchers have been working to predict both short and long term patient outcome after an index stroke. Understanding which patients will improve after rt-PA over the short and long term has been the focus of previous research, and relevant variables have been found. Both the baseline NIHSS[10,11] and mRS[12-14] have been shown to be

Table 2. *Outcomes among good (GR++) versus mixed (GR+/-) versus poor (GR- -) responders to rt-PA*

	GR++	GR+/-	GR- -	*P* Value
90-d functional status				< .001
mRS 0-2	25 (36.8)	6 (11.8)	0	
mRS > 2	43 (63.2)	45 (88.2)	29 (100)	
90-d mortality				.04
Alive	63 (92.6)	43 (86)	21 (72)	
Deaths	5 (7.4)	7 (14)	8 (27.6)	

Abbreviations: mRS; modified Rankin scale; rt-PA, recombinant tissue plasminogen activator.
Values expressed as no. (%) unless otherwise indicated.

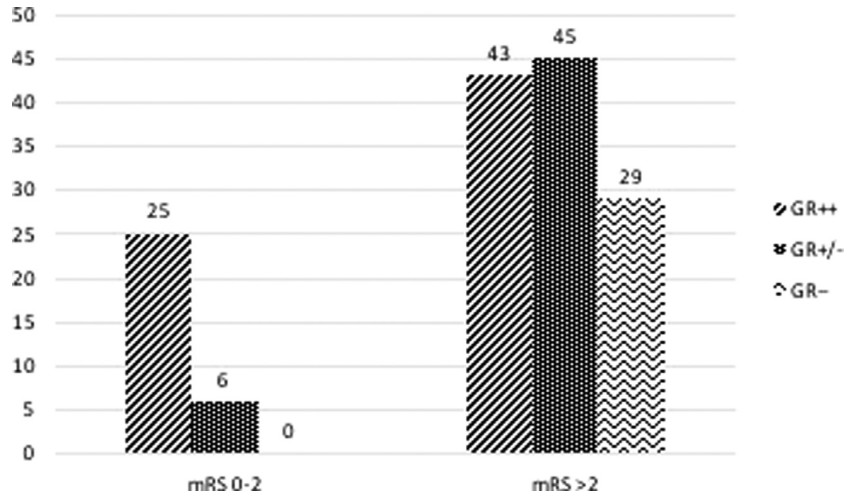

Figure 2. *90-day functional outcomes among good (GR++) versus mixed (GR+/-) versus poor (GR- -) responders (n = 148) to rt-PA. A favorable outcome was found to be statistically significant among GR++ compared to GR- - and GR+/- (P < 0.001). Abbreviations: mRS, modified Rankin scale; rt-PA, recombinant tissue plasminogen activator.*

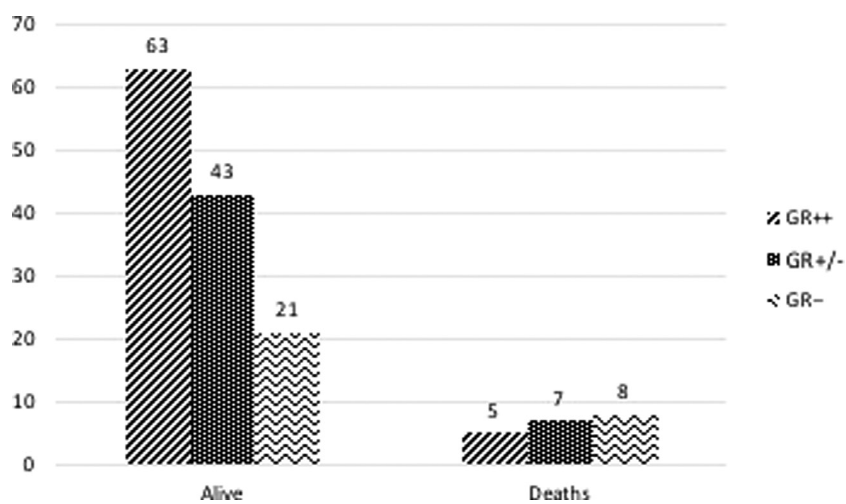

Figure 3. *90-day mortality outcomes among good (GR++) versus mixed (GR+/-) versus poor (GR- -) responders (n = 147) to rt-PA. There was a significant difference favoring GR++ compared to GR— and GR+/- (P = 0.04). Abbreviation: rt-PA, recombinant tissue plasminogen activator.*

predictors of long-term outcome, as has elevated admission glucose levels,[15-16] white matter changes,[18] and increased CHA_2DS_2VASc scores in atrial fibrillation patients.[19]

Prior literature has reported on variables that may be correlated with rapid neurologic recovery as well. Some relevant ones include clinical indices such as the NIHSS at 24 hours combined with 7 days[7] and pre-stroke mRS,[12-14] radiographic indices such as the size of the core stroke lesion on perfusion CT,[20] subsequent MRI,[21] or even biomarkers to predict outcome.[22] Other predictors of rapid neurologic recovery generally include age, admission glucose, time to treatment, and atrial fibrillation.[8]

Two issues with current predictive strategies include their complexity or need to obtain information over a longer period of time. We hypothesized that, using just 2 variables—hospital LOS of 3 days or less, and discharge destination of home—that can be obtained early in the spectrum of stroke care, post-thrombolytic stroke patients can be reliably identified that will go on to have favorable and sustained 90-day clinical outcomes. Our novel, and clinically relevant definition of GR++ that identified "good responders" to rt-PA, utilizes information that can easily be obtained during hospital stay, and is simple in its design.

Our goals were to determine the characteristics that make these GR++ rapid responders different, and determine if early rapid response to rt-PA would correlate with long term outcomes at 90 days. We found approximately 40% of patients in our sample were defined as being GR++, which is consistent with the 49% noted in other data sets.[7] Our value may be lower in that we required that patients did well early after rt-PA and also went directly home. GR++ patients were younger and more likely to have a low baseline mRS. Consistent with other literature, and likely resulting in longer hospital stays, presence of atrial fibrillation, symptomatic ICH, and baseline mRS greater than 2 were associated with "poor responders" to rt-PA.

Our definition strongly predicted 90-day outcomes after rt-PA. Mortality at 90 days was lower in GR++ with 93% of GR++ patients being alive at 90 days and 37% having mRS(0-2). We were unable to show that either of these 2 variables accounted for a preponderance of the outcome benefit noted, showing that both outcomes may, together, help provide a surrogate profile for sustained 90-day benefit.

Our study only analyzed acutely treated stroke patients from a stroke registry, and did not include untreated stroke patients, as we aimed to understand which characteristics are unique for these patients who may very quickly respond to rt-PA. In addition, as our secondary goal, we wanted to explore the prognostic significance of a good responder (GR++) profile (i.e., short LOS, and goes home directly) over poor responder (GR--) and mixed responders (GR+/-). Applying this proposed novel outcome measures tool to only treated stroke patients seemed appropriate for a preliminary study, as applying these measures over both treated and untreated patients may have been too perplexing.

With this in mind, we propose that subsequent analyses should include patients not treated with rt-PA, as part of extending the sample size to include the entire database and other affiliated hospitals, as so to increase generalizability.

Although small strokes would be expected to have lower NIHSS and likely have shorter lengths of stay and better discharge destinations after thrombolysis, we address this potential confounder by adjusting for baseline NIHSS, age, baseline glucose, and smoking status. Other limitations of our study include its retrospective design, clinical decision to include these 2 clinically chosen variables, and small sample size. Similarly, outcome prediction is likely straightforward given current medical infrastructure where discharge destinations and LOS can both be variable, based on socioeconomic issues or insurance status, increased complications, number of procedures, and bed availability. Further studies must be done to assess how these complex interactions contribute to the results.

In our analysis, we found that using just 2 variables that can be obtained early in the spectrum of stroke care, post-thrombolytic stroke patients can be identified that will go on to have favorable and sustained 90-day clinical outcomes. This observation alone cannot modify practice; however if this goes on to prove generalizable after further analyses in larger data sets, it would assist patients in understanding expectations for recovery. Similarly, it would help clinicians and the healthcare system in re-allocating limited rehabilitation resources to patients that otherwise might not have a good long term outcome.

Finally, its use could potentially be expanded to the clinical trial infrastructure to decrease the burden of performing actual 90-day follow ups to assess post-thrombolytic stroke patients for trial endpoints. This may have important implications for future clinical practice, clinical trial development, and resource allocations. Further work assessing validity, reliability, and generalizability is ongoing.

Declaration of Competing Interest

Dr. Brett Meyer receives grant support for U24NS107225. Dr. Dawn Meyer is on Speaker's Bureau for Portola and Chiesi. Dr. Alyssa Bautista discloses no conflict of interest.

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