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Time to Neurological Deterioration in Ischemic Stroke

James E. Siegler, MD[1†], Karen C. Albright, DO, MPH[2,3,4,5†], Alexander J. George, BS[1], Amelia K. Boehme, MSPH[2], Michael A. Gillette, MPH [1], Andre D. Kumar, MD[1], Monica Aswani MSPH[6], Sheryl Martin-Schild, MD, PhD[1*]

[1] Stroke Program, Department of Neurology, Tulane University Hospital, New Orleans, LA 70112.
[2] Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, 35294.
[3] Health Services and Outcomes Research Center for Outcome and Effectiveness Research and Education (COERE), University of Alabama at Birmingham, 35294.
[4] Center of Excellence in Comparative Effectiveness Research for Eliminating Disparities (CERED) Minority Health & Health Disparities Research Center (MHRC), University of Alabama at Birmingham, 35294.
[5] Department of Neurology, School of Medicine, University of Alabama at Birmingham, 35294.
[6] Department of Department of Health Care Organization and Policy, School of Public Health, University of Alabama at Birmingham, Birmingham, AL 35249.
[†] Siegler and Albright contributed equally to this article as first authors.

*Sheryl Martin-Schild, MD, PhD.
Stroke Program at Tulane University Hospital, Department of Neurology
1440 Canal Street, TB-52, Suite 1000
New Orleans, LA 70112-2715
504.988.0972 (phone)
504.988.6263 (fax)
smartin2@tulane.edu

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ABSTRACT

Background: Neurological deterioration (ND) is common, with nearly one-half of ND patients deteriorating within the first 24 to 48 hours of stroke. The timing of ND with respect to ND etiology and reversibility has not been investigated.

Methods: At our center, we define ND as an increase of 2 or more points in the National Institutes of Health Stroke Scale (NIHSS) score within 24 hours and categorize etiologies of ND according to clinical reversibility. ND etiologies were considered non-reversible if such causes may have produced or extended any areas of ischemic neurologic injury due to temporary or permanent impairment in cerebral perfusion.

Results: Seventy-one of 350 ischemic stroke patients experienced ND. Over half (54.9%) of the patients who experienced ND did so within the 48 hours of last seen normal. The median time to ND for non-reversible causes was 1.5 days (IQR 0.9, 2.4 days) versus 2.6 days for reversible causes (IQR 1.4, 5.5 days, p=0.011). After adjusting for NIHSS and hematocrit on admission, the log-normal survival model demonstrated that for each 1-year increase in a patient's age, we expect a 3.9% shorter time to ND (p=0.0257). In addition, adjusting for age and hematocrit on admission, we found that that for each 1-point increase in the admission NIHSS, we expect a 3.1% shorter time to ND (p=0.0034).

Conclusions: We found that despite having similar stroke severity and age, patients with nonreversible causes of ND had significantly shorter median time to ND when compared to patients with reversible causes of ND.

INTRODUCTION

Neurological deterioration (ND) following acute ischemic stroke is common, occurring in up to 40% of acute ischemic stroke patients.[1] While various definitions of neurologic deterioration have been utilized throughout the literature and no consensus has been reached,[2] our center has defined neurologic deterioration as an increase in the National Institutes of Health Stroke Scale (NIHSS) score (stroke severity score, with higher scores representing more severe strokes) by 2 or more points within a 24-hour period during hospitalization.[3] As we and others have shown, even a small worsening in NIHSS (as few as 2 points) has been associated with poorer prognosis when compared to patients who do not deteriorate.[3,4] Previous studies have shown the association between ND occurrence and stroke severity on admission,[5,6] the presence of large vessel occlusion,[7-9] history of coronary artery disease or myocardial infarction,[1,7] diabetes mellitus,[1,7,9,10] acute or chronic hyperglycemia,[1,7,11-13] elevated blood pressure,[13,14] as well as early recurrent ischemic stroke[15] and symptomatic intracranial hemorrhage (sICH).[11,16]

While it has been shown that nearly one-half of ND patients deteriorate within the first 24-48 hours of the stroke,[1,17-19] no study has described time to ND or investigated factors affecting time to ND. The primary objective of this study was to evaluate time to ND in ischemic stroke patients and to elucidate factors affecting time to ND. Our secondary objective was to determine if time to ND differed between patients with nonreversible and reversible causes of ND.

METHODS

Study Population and Data Source

Our hospital is a tertiary care referral center located in New Orleans which manages local patients in southern Louisiana as well as referred patients from facilities throughout the southeastern United States. All patients admitted to our center from June 2008 to December 2010 were screened via a prospective stroke patient registry as previously described.[20] This included direct hospital admissions, emergency department admissions, and transfers to our center from other hospitals. Only White and Black patients with ischemic stroke were included, as they represented the overwhelming majority of our center's patient population. For the purposes of this study, patients with an unknown time of last seen normal (LSN) or LSN over 48 hours prior to arrival, who experienced an in-hospital stroke, or who had incomplete time data were excluded. Patients who met inclusion criteria were monitored until the time of discharge for ND.

Variable Selection and Definition

We examined baseline characteristics, past medical history, home medication use, clinical presentation, stroke severity as measured by NIHSS, and laboratory findings, first by ND status and then by reversibility of ND etiology as part of a post hoc analysis of one previous investigation.[3] At our center, NIHSS on admission is determined during the first clinical encounter by the neurology resident (certified in NIHSS scoring) while subsequent NIHSS scores are determined daily by the neurology resident (and corroborated by the neurovascular attending) during morning rounds. If an episode of clinical deterioration is witnessed by other house staff, nursing staff, or other hospital team members, the event is recorded in the patient

medical record along with an updated NIHSS score. To be classified as having an ischemic stroke, patients had to meet both clinical and imaging (tissue-based) criteria. ND was defined as an increase of 2 or more points on a patient's NIHSS within a 24-hour period, as previously described since this threshold has been associated with several poor outcome measures including discharge disability and death.[3] We used previously described etiologies as defined by Siegler et al.[21] Patients with ND secondary to progressive stroke, new stroke, or intracerebral hemorrhage were classified as having nonreversible ND due to the fact that these etiologies may produce or extend any areas of ischemic neurologic injury from temporary or permanent impairment in cerebral perfusion (in keeping with our prior definitions).[6,21] Patients with ND secondary to edema, fluctuation in symptoms, seizure, extubation, sedation, or any hemodynamic, toxic, metabolic, or infectious etiology were classified as having a reversible cause of ND.[21] Several etiologies of clinical deterioration after stroke have been previously investigated,[2,22,23] but this does not encompass all potential causes of ND. Selected etiologies of ND for this investigation have been previously described at our center, classified as reversible or nonreversible, and were defined in a codebook prior to data abstraction from medical records in order to reduce the potential for bias.[6,21] Stroke etiology was defined according to the Trial of Org 10172 for Acute Stroke Treatment (TOAST).[24] Vascular risk factors were defined in keeping with previous definitions.[25]

Statistical Analysis

Categorical variables were compared using Pearson Chi-Square or Fisher's exact test where appropriate. Continuous variables were compared using the Wilcoxon Rank Sum test. We used Akaike information criterion (AIC), Baysian information criterion (BIC), probability plots, and

Cox-Snell residual plots to determine the best fitting parametric model. Once deemed appropriate, we then used log-normal distribution to determine the median time to ND and to determine which covariates significantly affected time to ND. Additionally, a multivariable Cox proportional hazards regression model was performed to evaluate median time to ND accounting for covariates. Kaplan-Meier analysis was used to estimate the time to ND for nonreversible and reversible causes. The log rank test was used to compare time to ND for ND resulting from any nonreversible cause and ND resulting from any reversible cause. The log normal distribution was also used to compare time to ND in nonreversible and reversible etiologies. As this was an exploratory analysis, no adjustments were made for multiple comparisons.[26] Two-sided *p* values of ≤ 0.05 were considered statistically significant. This study was approved by our center's Institutional Review Board.

RESULTS

During the 31-month period, 350 ischemic stroke (IS) patients were screened. Two hundred and ninety-nine met inclusion criteria. A comparison of patients who did not experience ND to those that had ND is depicted in Table 1. Patients who experienced ND were significantly older (73 v. 62 years, $p<0.001$), had higher systolic blood pressure on admission (173 vs. 159, $p=0.019$), higher NIHSS on admission (12 vs. 5, $p<0.001$), higher admission glucose (120 vs. 113, $p=0.055$), and higher HbA1c levels on admission (6.1 vs. 5.8, $p=0.027$).

A total of 71 patients experienced ND. The remaining 228 patients were categorized as censored (76.3%). Over half (54.9%, 39/71) of the patients who experienced ND did so within the 48 hours of LSN, with 25.4% (18/71) occurring within the first 24 hours. As shown in Figure 1, the observed mean time to ND for the 71 patients that experienced ND was 20 days.

By 5.5 days, 25% of the sampled patients had experienced ND. Of all potential covariates, only age, NIHSS on admission, and admission hematocrit (Hct) were significant predictors of time to ND in univariate analysis. After adjusting for NIHSS and Hct on admission, survival analysis using the log-normal model demonstrated that for each 1-year increase in a patient's age, we expect a 3.9% shorter time to ND (p=0.0257). In addition, adjusting for age and Hct on admission, we found that that for each 1-point increase in the admission NIHSS, we expect a 3.1% shorter time to ND (p=0.0034). After adjusting for age and NIHSS on admission, Hct on admission did not reach statistical significance (p=0.0738).

Table 2 contrasts patients who experienced ND from non-reversible causes (i.e., new stroke, stroke progression, hemorrhagic transformation) and reversible causes (e.g., edema, toxic, metabolic, infectious). Patients who experienced reversible ND were more frequently black (85.2% vs. 59.0%, p=0.030), reported higher rates of prior stroke (48.1% vs. 23.1%, p=0.034), dyslipidemia (57.7% vs. 25.6%, p=0.009), while patients who experienced ND from non-reversible causes were more frequently treated with IV t-PA (46.2% vs. 22.2%, p=0.047). Two thirds of patients with ND from a nonreversible cause experienced ND within 48 hours of LSN (66.7%, 26/39), with 13 of these events occurring within 24 hours (33.3%, 13/39). Over one third of the patients who experienced ND of reversible cause did so within the 48 hours of LSN (37.0%, 10/27), with 14.8% (4/27) occurring within the first 24 hours. As demonstrated in Figure 2, Kaplan Meier analysis was used to assess time to ND between patients with reversible causes of ND and nonreversible causes of ND. The curves appear to differentiate after 1 day with ND of nonreversible cause falling more steeply (Log Rank p=0.007). The median time to ND for non-reversible causes was 1.5 days (IQR 0.9, 2.4 days), while the median time to ND for reversible causes was 2.6 days (IQR 1.4, 5.5 days, p=0.011).

DISCUSSION

To the best of our knowledge, this is the first study to apply parametric models from survival analysis to examine time to ND and factors affecting time to ND in ischemic stroke patients. In our sample, higher NIHSS on admission and older age were associated with shorter time to ND. In keeping with previous reports, we found that over half of the patients who experienced ND did so within the 48 hours of LSN.[1,17-19] Beyond previous studies, we found the mean time to ND to be 20 days, with 25% occurring by 5.5 days. In addition, we found that despite having similar stroke severity and age, patients with nonreversible causes of ND had significantly shorter median time to ND when compared to patients with reversible causes of ND.

Our study has several limitations. The definition of ND at our center (2 point deterioration over a 24 hour period) may be more lenient than others.[2] However, as discussed above, we have found that even a 2-point increase in the NIHSS is clinically significant and may lead to disability or even in-hospital death and therefore should not be discounted. As our standard is to perform the NIHSS in order to assess for ND each morning prior to attending rounds, our ability to measure the precise time each ND actually occurred is less granular than desired. Certain instances of ND (such as ND due to cardiopulmonary arrest) were likely documented with greater temporal precision due to the acuteness and severity of this type of clinical deterioration. In contrast, other etiologies of ND (such as ND due to stroke progression) may be milder or subclinical and only detectable during a physician's neurological examination. Certainly, because a majority of episodes of ND occurred during the first 24-48 hours of hospitalization, more frequent NIHSS examinations may be warranted. We plan to explore this in future investigations. In addition, our sample includes only White and Black Americans raising questions about its generalizability to other ethnic and racial groups. Further, we

included only patients with last seen normal times within 48 hours of arrival, limiting the ability to generalize our findings to non-acute patients. Finally, we are limited by our relatively small number of recorded events.

Despite these limitations, our study is unique in that it describes actual time to ND and factors affecting time to ND. Further, we found that patients with nonreversible causes of ND have shorter times to ND than those with reversible causes of ND. Larger prospective studies are needed to confirm our findings. If the average time to ND is 20 days, a time after the majority of patients have been discharged from the stroke unit, then additional training on the signs of ND may be warranted for rehabilitation specialists and family members. If other studies confirm that nonreversible causes of ND occur significantly earlier than reversible causes, then this information could be used to create stroke unit protocols outlining more frequent reassessment of the NIHSS examination and the order in which diagnostic studies should be performed to determine the cause of ND.

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TABLES and FIGURES

Table 1: Demographics and clinical presentation of patients who did not experience neurological deterioration (ND) compared to patients who experienced ND.

	No ND n=228	ND n=71	p value
Age, median years (range), IQR	62 (19-97) 53,74	73 (39-92) 61,81	**<0.001**
Gender, No. female (%)	94 (41.2)	30 (42.1)	0.878
Race, No. (%) patients			0.649
Black	154 (67.5)	50 (70.4)	
White	74 (32.5)	21 (29.6)	
Past Medical History, No. (%)			
Stroke	92 (40.4)	25 (35.2)	0.438
Carotid Artery Stenosis >50%	38 (17.5)	17 (27.0)	0.096
Atrial Fibrillation	21 (9.3)	8 (11.4)	0.607
Hypertension	169 (74.4)	58 (82.9)	0.147
Diabetes	71 (31.3)	27 (38.6)	0.257
Hyperlipidemia	101 (44.9)	27 (38.6)	0.352
Coronary Artery Disease	38 (16.7)	16 (22.5)	0.262
Systolic Heart Failure	19 (8.4)	4 (5.7)	0.612
Home Medications, No. (%)			
Anti-platelet Agent	87 (38.7)	33 (46.5)	0.242
Anti-hypertensive Agent	145 (64.4)	51 (75.0)	0.105
Oral Diabetes Medication	46 (20.3)	16 (23.5)	0.562
Lipid-lowering Agent	90 (39.8)	27 (39.7)	0.986
Active Smoker, No. (%)	72 (31.9)	18 (25.7)	0.329
SBP, median mmHg (range), IQR	159 (96-280) 139,185	173 (107-234) 145,200	**0.019**
DBP, median mmHg (range), IQR	94 (54-180) 83,107	93 (60-179) 82,118	0.221

Admission NIHSS, median (range), IQR	5 (0-29) 3,10	12 (0-29) 5,20	<**0.001**
Admission Glucose, median mg/dL (range), IQR	113 (70-569) 95,143	120 (78-391) 102,148	**0.055**
Treatment, No. (%)			
IV t-PA	78 (34.5)	26 (36.6)	0.746
IAT	7 (3.1)	6 (8.5)	0.054
LDL, median mg/dL (range), IQR	103 (17-540) 77,128	120 (29-540) 72,150	0.149
HbA1c, median % (range), IQR	5.8 (5.0-14.0) 5.4,6.6	6.1 (5.0-13.0) 5.7,6.5	**0.027**
24hr NIHSS, median (range), IQR	2 (0-29) 1,6	13 (1-42) 5,21	<**0.001**
TOAST, No. (%)			0.301
Cardioembolic	59 (25.9)	21 (29.6)	
Large Vessel	52 (22.8)	22 (31.0)	
Small Vessel	45 (19.7)	15 (21.1)	
Cryptogenic (>1 cause)	7 (3.1)	2 (2.8)	
Cryptogenic (no cause)	55 (24.1)	8 (11.3)	
Other	10 (4.4)	3 (4.2)	

ND denotes neurological deterioration, IQR interquartile range, SBP systolic blood pressure, DBP diastolic blood pressure, National Institutes of Health Stroke Scale, IV t-PA intravenous tissue-plasminogen activator, IAT intra-arterial thrombolysis, LDL low density lipoprotein, HbA1c hemoglobin A1C, and TOAST Trial of org 10172 in acute stroke treatment.

Table 2: Demographics and clinical presentation of patients who experienced a non-reversible cause of ND compared to patients who experienced ND of reversible cause.

	Non-reversible n=39	Reversible n=27	p value
Age, median y (range), IQR	75 (39-89) 66,79	66 (42-89) 59,81	0.177
Gender, No. female (%)	17 (43.6)	12 (44.4)	0.945
Race, No. (%) patients			**0.030**
Black	23 (59.0)	23 (85.2)	
White	16 (41.0)	4 (14.8)	
Past Medical History, No. (%)			
Stroke	9 (23.1)	13 (48.1)	**0.034**
Carotid Artery Stenosis >50%	11 (32.4)	5 (20.8)	0.385
Atrial Fibrillation	5 (12.8)	3 (11.5)	1.000
Hypertension	30 (76.9)	24 (92.3)	0.177
Diabetes	12 (30.8)	12 (46.2)	0.208
Hyperlipidemia	10 (25.6)	15 (57.7)	**0.009**
Coronary Artery Disease	5 (15.4)	9 (33.3)	0.087
Systolic Heart Failure	3 (7.7)	1 (3.8)	0.644
Home Medications, No. (%)			
Anti-platelet Agent	15 (38.5)	15 (55.6)	0.170
Anti-hypertensive Agent	26 (68.4)	21 (84.0)	0.239
Oral Diabetes Medication	7 (18.4)	7 (28.0)	0.371
Lipid-lowering Agent	12 (31.6)	13 (52.0)	0.105
Active Smoker, No. (%)	9 (23.1)	7 (26.9)	0.724
SBP, median mmHg (range), IQR	175 (122-234) 149,205	176 (107-207) 146,195	0.554
DBP, median mmHg (range), IQR	90 (60-139) 82,117	95 (68-139) 86,120	0.689
Admission NIHSS, median (range), IQR	11 (0-26) 4,18	10 (0-29) 5,20	0.819

Admission Glucose, median mg/dL (range), IQR	122 (79-391) 105,151	108 (78-291) 95,151	0.208
Treatment, No. (%)			
IV t-PA	18 (46.2)	6 (22.2)	**0.047**
IAT	5 (12.8)	1 (3.7)	0.388
LDL, median mg/dL (range), IQR	121 (29-210) 73,142	92 (37-540) 70,164	0.940
HbA1c, median % (range), IQR	6.1 (5.0-12.0) 5.7,6.4	6.0 (5.0-13.0) 5.8,6.8	0.701
24hr NIHSS, median (range), IQR	12 (1-42) 5,20	14 (2-27) 4,21	0.504
TOAST, No. (%)			0.211
Cardioembolic	12 (30.8)	7 (25.9)	
Large Vessel	13 (33.3)	8 (29.6)	
Small Vessel	7 (17.9)	7 (25.9)	
Cryptogenic (>1 cause)	1 (2.6)	1 (3.7)	
Cryptogenic (no cause)	6 (15.4)	1 (3.7)	
Other	0 (0)	3 (11.1)	

Reversible and non-reversible causes of ND are described in the text. ND denotes neurological deterioration, IQR interquartile range, SBP systolic blood pressure, DBP diastolic blood pressure, National Institutes of Health Stroke Scale, IV t-PA intravenous tissue-plasminogen activator, IAT intra-arterial thrombolysis, LDL low density lipoprotein, HbA1c hemoglobin A1C, and TOAST Trial of org 10172 in acute stroke treatment.

Figure 1: Log normal (parametric) survival curve demonstrating time to neurological deterioration with Cox proportional hazards curve overlaid. Figure demonstrates the time to neurological deterioration using two separate models.

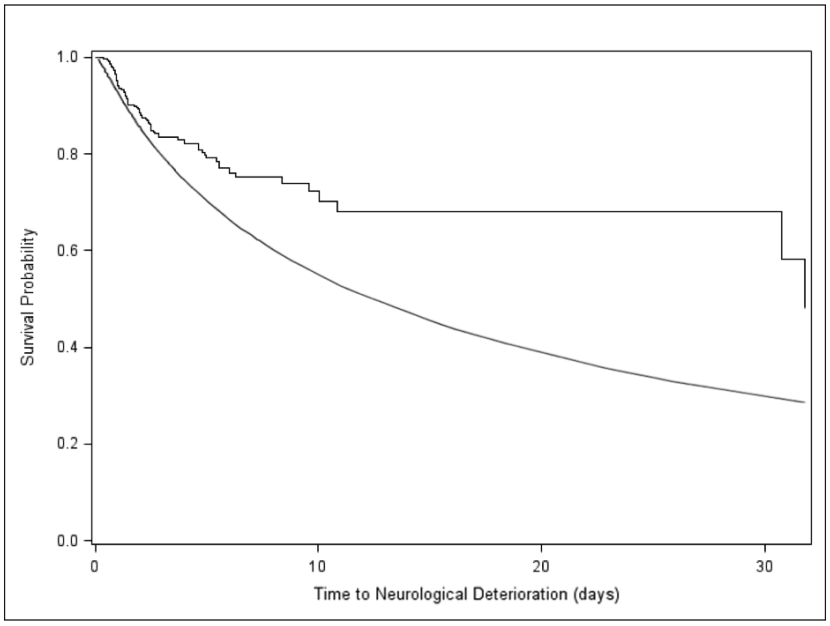

Figure 2: Kaplan Meier survival curve comparing time to neurological deterioration for patients with non-reversible causes of ND to patients with reversible causes of ND with log normal curves overlaid. Figure depicts Kaplan Meier and log normal curves evaluating differences in time to neurological deterioration according to reversible and non-reversible etiologies. Log Rank p=0.007 for differences.