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# Identification of modifiable and non-modifiable risk factors for neurological deterioration following acute ischemic stroke

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## Abstract

**Introduction—**Neurological deterioration (ND) following ischemic stroke has been shown to impact short-term functional outcome and is associated with in-hospital mortality.

**Methods—**Patients with acute ischemic stroke who presented between 07/08–12/10 were identified and excluded for in-hospital stroke, presentation >48hrs since last seen normal, or unknown time of last seen normal. Clinical and laboratory data, National Institutes of Health Stroke Scale (NIHSS) scores, and episodes of ND (increase in NIHSS score ≥2 within a 24hr period) were investigated.

**Results—**Of the 596 patients screened, 366 were included (median age 65 y, 42.1% female, 65.3% black). Of these, 35.0% experienced ND. Patients with ND were older (69 vs. 62 y, p<0.0001), had more severe strokes (median admission NIHSS 12 vs. 5, p<0.0001), carotid artery stenosis (27.0% vs. 16.8%, p=0.0275), and coronary artery disease (26.0% vs. 16.4%, p=0.0282) compared to patients without ND. Patients with ND had higher serum glucose on admission than patients without ND (125.5 vs. 114 mg/dL, p=0.0036). After adjusting for crude variables associated with ND, age >65 and baseline NIHSS>14 remained significant independent predictors of ND. In a logistic regression analysis adjusting for age and serum glucose, each 1-point increase in admission NIHSS was associated with a 7% increase in the odds of ND (OR 1.07 95%CI 1.04-1.10, p<0.0001).

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**Conclusions—**Older patients and patients with more severe strokes are more likely to experience ND. Initial stroke severity was the only significant, independent, and modifiable risk factor for ND, amenable to recanalization and reperfusion.

### Keywords

Acute ischemic stroke; neurological deterioration; risk factors; outcome

## INTRODUCTION

Roughly one-third of patients who suffer from acute ischemic stroke will clinically deteriorate in the days following hospital admission.(1, 2) These patients are known to have worse functional and neurological outcome in both the short-term(3) and long-term.(4)

Several risk factors for neurological worsening have been previously described. These risk factors include stroke severity,(2, 3) elevated serum glucose on admission,(2) elevated leukocyte count,(5, 6) low serum hemoglobin,(7) internal carotid artery occlusion,(8) brainstem infarction,(8) significant depression in systolic blood pressure(9) or elevation in systolic blood pressure(2, 9, 10), diabetes mellitus,(8) atrial fibrillation,(3, 11) and others,(3, 6, 12, 13) but these associations have not been repeatedly demonstrated throughout additional studies. The aim of this investigation was to identify risk factors for clinical deterioration following acute ischemic stroke using a validated definition of ND.(14) All proposed definitions of ND have been shown to negatively impact prognosis. We recently validated a sensitive definition of ND for several poor outcome measures such as poor functional outcome at discharge (discharge modified Rankin Scale score >2) and in-hospital mortality.(14)

## METHODS

We conducted a single-center retrospective analysis of all consecutive patients who presented with acute ischemic stroke between July 2008 and December 2010. Patients were excluded if they presented >48 hours after last seen normal (LSN) or had an unknown time of LSN. Patients with an in-hospital stroke were also excluded because their primary illness, which necessitated hospital admission, may have impacted their risk of ND. ND was defined as an increase in the National Institute of Health Stroke Scale (NIHSS) score of 2 or more points in a 24-hour period during hospitalization, as per our prior investigations.(14, 15) Stroke etiologies were stratified according to those previously described in the Trial of Org 10172 in Acute Stroke Treatment (TOAST).(16) Pertinent past medical history data were documented if reported by the patient during the initial history and physical exam. A positive history of stroke was documented if prior infarcts or hemorrhages were identified on neuroimaging modalities during the patient's current hospitalization for stroke. Modifiable risk factors were defined as historical or medical data elements that may be related to ND, and had to have been present and preventable before the stroke occurred but not preventable after the index stroke event (e.g. history of hypertension or diabetes). Similarly, non-modifiable risk factors were defined as historical or medical data elements that must have been present before the stroke occurred and could not have been prevented (e.g. age, infarct location). Carotid artery stenosis was defined as >50% reduction in internal carotid artery lumen based on carotid duplex imaging, computed tomography angiography or contrast-enhanced magnetic resonance angiography, using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) methodology.(17) Infarct location (cortical vs. non-cortical) and stroke vessel distribution was determined by a board-certified vascular neurologist using diffusion-weighted imaging sequence of magnetic resonance imaging of the brain. NIHSS examinations were performed by an NIHSS certified neurology

attending and/or house officer. A modified Rankin Scale (mRS) score was documented for each patient upon discharge by a mRS-certified(18, 19) neurology attending.

Categorical data were presented as frequencies and compared using Pearson Chi-squared or Fisher exact test where appropriate. Continuous data are represented as a median with ranges and compared using Wilcoxon Rank Sum test. Further associations were investigated using logistic regression, categorizing variables of interest and adjusting for covariates. Additionally, we used a logistic regression analysis to determine the odds of ND for every point increase in the NIHSS, with the NIHSS as a continuous variable, after adjusting for age and admission serum glucose level. All tests were performed at the $\alpha$=0.05 level and were two sided.

## RESULTS

Of the 596 patients screened, 366 met inclusion criteria (median age 65 years, 42.1% female, 65.3% black). Of these, 128 (35.0%) experienced ND according to our definition. Patients with ND were more likely to be over 65 (unadjusted OR=2.20 95%CI 1.41-3.43, p=0.0005). In a comparison where patients were stratified according to admission NIHSS using three categories as previously described (<7, 7-14, and >14)(20) using admission NIHSS of <7 as the referent group, patients with admission NIHSS 7-14 were two times as likely to experience ND (unadjusted OR=2.10 95%CI 1.20-3.60, p=0.7799), while patients with admission NIHSS >14 were nearly four times as likely to experience ND (unadjusted OR=3.90 95%CI 2.30-6.80, p<0.0001, Table 1). Patients with a history of coronary artery disease were nearly two times more likely to experience ND than patients without coronary artery disease (unadjusted OR=1.80 95%CI 1.10-3.00, p=0.0294, Table 1). While no difference was found regarding the prevalence of diabetes in patients with ND versus those without ND, patients with ND were more likely to have higher serum glucose on admission than patients without ND (median glucose level 125.5 vs. 114 mg/dL, p=0.0036, Table 2).

Among infarct locations, the unadjusted odds of experiencing ND was greater in patients with cortical (unadjusted OR=1.60 95%CI 1.00-2.60, p=0.0457) or anterior cerebral artery infarcts (unadjusted OR=3.63 95%CI 1.31-10.07, p=0.0131) in contrast to non-cortical strokes and strokes in other vessel territories (Table 3). Compared to other vessel territories, middle cerebral artery infarctions were more likely to be associated with ND, but this did not reach statistical significance (unadjusted OR=1.50 95%CI 0.96-2.38, p=0.0714). The presence of carotid stenosis was found to be a risk factor for ND (unadjusted OR=1.80 95%CI 1.10-3.10, p=0.0298), and interestingly, this relationship remained independent regardless of the side of the stenosis in relation to the side of the cerebral infarct (Table 3).

Combining the aforementioned risk factors for ND with adjustment for covariates, we found that age >65 years (OR 1.79 95%CI 1.11-2.93, p=0.0178) and baseline NIHSS >14 (OR 2.64 95%CI 1.56-4.49, p=0.0003) were the two significant predictors of ND (Table 4). When combining the most significant risk factors for ND, the odds of ND are greatest for patients 65 years old or younger with a baseline NIHSS >14, however patients older than 65 years with a baseline NIHSS >14 are also at significant odds of ND (Table 5). Using a logistic regression model where admission NIHSS was assessed as a continuous variable, each single point increase in a patient's admission NIHSS is associated with a 7% greater odds of ND after adjusting for admission serum glucose and age (OR=1.07, 95%CI=1.04-1.10, p<0.001).

## DISCUSSION

Neurological deterioration is a common, debilitating process that often occurs during the first several days following an acute stroke. Even a subtle 2-point increase in the NIHSS (out of 42 points) in a 24 hour period is predictive of poor functional outcome and all cause in-hospital mortality in patients with stroke.(14) Using this 2-point threshold for a change in NIHSS as a definition for ND, we aimed to identify the modifiable and non-modifiable risk factors for this deleterious process that occurs in up to one-third of patients who suffer from stroke.

### Non-modifiable risk factors for ND

The most significant, independent risk factors for ND were age older than 65 years and greater stroke severity (baseline NIHSS >14), with stroke severity having the greatest odds of predicting ND. Older age is a known predictor of poor outcome in cerebrovascular(21) and cardiovascular disease,(22) perhaps due to the greater number of or more advanced comorbidities associated with older age. More severe strokes correlate clinically with worse functional deficits(23) and a higher mortality.(24) The risk of ND associated with greater admission NIHSS may be due to the fact that NIHSS correlates with infarct volume during the acute phase of stroke,(25) and larger stroke volumes are associated with greater risk of developing edema. Interestingly, in our analysis we found that each additional point higher on a patient's admission NIHSS confers a 7% increase in the odds of that patient experiencing ND, and therefore poor outcome. This can be illustrated by the following example: A more severe stroke (higher NIHSS) may result in severe limitation of lower extremity strength, thereby reducing mobility and increasing the risk of deep venous thromboses and pulmonary embolism, with associated morbidity and mortality. The higher likelihood of post-stroke mortality among older patients and patients with more severe strokes understandably contributes to a greater proportion of patients with worsening NIHSS and ND. When evaluating the type of stroke, we found that anterior cerebral artery infarcts were more significantly associated with ND than infarcts in other vessel territories. This is in keeping with the findings of Kwan *et al.*(3), however this may be a chance finding in our investigation due to the low proportion of patients with anterior cerebral artery infarcts.

A study by Bang *et al.* reported that a greater proportion of patients with territorially distributed and internal border zone (periventricular white matter) infarcts experienced an "unstable hospital course" (fluctuating or worsening neurological status), compared to patients with purely cortical involvement on diffusion-weighted imaging.(26) Contrary to this and other reports,(27) we observed a higher proportion of patients with ND had experienced cortical infarctions, rather than solely sub-cortical or cerebellar infarctions. However, our study is limited in the fact that we did not distinguish infarct locations using the 6 different lesion patterns as described by Bang *et al.* This may help to explain the differences between the results of our studies as a large number of patients in our population with cortical infarcts also had local white matter extension of the original infarction. Because of the difference in our methods, it is difficult to compare the results between our studies.

In our sample, we were unable to confirm previously reported findings associating ND with elevated leukocyte count, low serum hemoglobin, internal carotid artery occlusion, brainstem infarction, abnormally elevated or depressed blood pressure, diabetes mellitus, or atrial fibrillation. However, none of the remaining demographic measures we investigated were found to clinically impact ND.

### Modifiable risk factors for ND

We confirmed that history of coronary artery disease, which has been shown previously in the European Cooperative Acute Stroke Study (ECASS) to be a predictor of early progressive stroke,(28) is associated with an increased odds of ND using our definition of ND. Similarly, the presence of carotid stenosis was associated with an increased odds of ND. Carotid stenosis has been previously demonstrated to impact stroke severity(29) and prognosis(30) regardless of treatment during the acute period of stroke. Therefore, it was expected that the presence of carotid stenosis during an acute stroke would negatively affect outcome in our patients. While coronary artery disease and carotid stenosis were found in the univariate model to be risk factors for ND, this may be due to the underlying relationship between these comorbidities and embolic cerebral occlusions, which may cause more severe strokes than intrinsic small vessel disease. This may explain why these risk factors lose significance in the multi-variate model, where baseline stroke severity remains independently associated with ND. Additionally, because carotid stenosis was associated with ND regardless of the location of the stenosis, we also speculate that carotid stenosis (like coronary artery disease) may be a marker for chronic microvascular disease.(31)

While we did not observe that a history of diabetes (irrespective of type) was associated with ND, we did find that higher serum glucose levels on admission were associated with ND in concordance with prior studies.(27, 32, 33) It is currently theorized that stress hyperglycemia may be the mechanism behind worse outcome following stroke(34, 35) and that this effect is independent of the patient's clinical history of diabetes. We found this is consistent with data from our sample and demonstrated that acute hyperglycemia during the early phase of a cerebral infarct is significantly associated with ND. Hyperglycemia has consistently been demonstrated as a risk factor for poor outcome, but convincing evidence that hyperglycemia is a modifiable risk factor for poor outcome is lacking. Whether modifiable or a marker for poor outcome, hyperglycemia is treated in our center at a threshold of 160 mg/dL.

In our sample, we were unable to confirm atrial fibrillation as a predictor for clinical deterioration following stroke.(3) One possible explanation is that our study had a lower proportion of patients with atrial fibrillation (12.8% with ND, 9.4% without ND), as opposed to the proportions reported by Kwan *et al.* (33% with ND, 16% without ND).

Although our study is limited by its small sample size and retrospective nature, it is unique in its use of a standardized definition of ND. This 2-point definition of ND has been shown to have significant prognostic value for clinicians who evaluate and treat patients with acute ischemic stroke.(14) Our data is also limited by the absence of several data elements (such as history of obstructive sleep apnea) that could have been investigated for their relationship with ND. However, our data is also unique due to the fact that we capture daily NIHSS scores thereby permitting collection of ND events without abstraction from the clinical exam components.

In conclusion, our study found the only significant, independent risk factors for ND are age and initial stroke severity. Only stroke severity is potentially modifiable by early revascularization and reperfusion. Therefore, we believe the best way to reduce the likelihood of early clinical decline following acute ischemic stroke is to reduce the initial stroke severity by achieving early reperfusion with intravenous thrombolysis or intra-arterial therapy.

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**DISCLOSURES**

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**Table 1**

Demographic information and past medical history.

| | **No ND N=238** | **ND N=128** | **P value** |
|---|---|---|---|
| Age, median years (range) | 62 (19-97) | 69 (28-96) | **<0.0001** |
| Gender, No. female (%) | 100 (42.0%) | 54 (42.2%) | 0.9748 |
| Race, No. (%) | | | 0.4478 |
| White | 73 (30.9%) | 38 (29.7%) | |
| Black | 151 (64.0%) | 88 (68.8%) | |
| Hispanic | 7 (3.0%) | 2 (1.5%) | |
| Other | 5 (2.1%) | 0 (0.0%) | |
| Past Medical History, No. (%) | | | |
| Stroke | 92 (38.7%) | 55 (43.0%) | 0.4221 |
| Coronary Artery Disease | 39 (16.4%) | 33 (26.0%) | **0.0282** |
| Atrial Fibrillation | 22 (9.4%) | 16 (12.8%) | 0.3121 |
| Diabetes Mellitus | 74 (31.2%) | 46 (36.5%) | 0.3083 |
| Hypertension | 179 (75.5%) | 99 (79.2%) | 0.4313 |
| Dyslipidemia | 107 (45.5%) | 51 (40.8%) | 0.3891 |
| Cancer (prior or active) | 21 (8.8%) | 14 (10.9%) | 0.5119 |
| Active Smoker | 74 (31.5%) | 29 (23.6%) | 0.1163 |
| Smoker in last year | 79 (33.8%) | 31 (25.4%) | 0.1056 |

Abbreviations: ND, neurological deterioration.

## Table 2

Admission laboratory data.

| | No ND N=238 | ND N=128 | P value |
|---|---|---|---|
| Admission Labs, median (range) | | | |
| Serum glucose, mg/dL | 114 (72-569) | 125.5 (76-663) | **0.0036** |
| Hematocrit, % | 39.4 (21.5-52.9) | 39.8 (24.2-52.3) | 0.5440 |
| WBC, $\times 10^3$/mL | 7.7 (3.3-22.3) | 8.0 (3.7-38.8) | 0.9719 |
| Platelets, $\times 10^3$/mL | 225 (83-599) | 221 (10-756) | 0.2243 |
| HDL, mg/dL | 42 (19-97) | 45 (11-100) | 0.1876 |
| LDL, mg/dL | 105 (17-223) | 103 (29-299) | 0.3318 |
| Triglycerides, mg/dL | 104.5 (16-683) | 91 (26-459) | 0.2640 |
| Cholesterol, mg/dL | 167 (47-309) | 166 (52-403) | 0.2576 |
| Magnesium, mg/dL | 2 (1.1-3.3) | 2 (0.6-2.9) | 0.6423 |
| Calcium, mg/dL | 9.0 (6.7-11) | 9.1 (5.0-10.5) | 0.7625 |
| INR, ratio | 1.0 (0.7-3.6) | 1.0 (0.9-2.2) | 0.9788 |
| PT, seconds | 10.7 (9.5-40.9) | 10.9 (1.4-21.5) | 0.9755 |
| PTT, seconds | 24.6 (12.1-38.0) | 23.8 (16.7-77.5) | **0.0361** |

Abbreviations: ND, neurological deterioration; WBC, white blood cell count; HDL, high density lipoprotein; LDL, low density lipoprotein; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time.

## Table 3

Stroke data.

| | No ND N=238 | ND N=128 | P value |
|---|---|---|---|
| Delay from LSN to ED arrival, median min (range) | 278.5 (10-2870) | 207 (15-2820) | 0.4473 |
| TOAST, No. (%) | | | 0.1038 |
| Cardioembolic | 61 (25.6) | 42 (32.8) | |
| Large Vessel | 55 (23.1) | 37 (28.9) | |
| Small Vessel | 48 (20.2) | 27 (21.1) | |
| >1 cause | 57 (23.9) | 13 (10.1) | |
| No cause | 7 (3.0) | 2 (1.6) | |
| Other | 10 (4.2) | 7 (5.5) | |
| Vessel Occlusion, No. (%) | | | |
| MCA | 119 (53.6) | 78 (63.4) | 0.0707 |
| ACA | 14 (6.3) | 16 (13.0) | **0.0332** |
| PCA | 22 (9.9) | 13 (9.8) | 0.8354 |
| Watershed | 0 (0.0) | 1 (0.8) | 0.4019 |
| PICA | 6 (2.7) | 1 (0.8) | 0.1701 |
| AICA | 2 (0.9) | 0 (0.0) | 0.4147 |
| SCA | 7 (3.2) | 5 (4.1) | 0.2110 |
| Vertebral | 4 (1.8) | 3 (2.4) | 0.6832 |
| Basilar | 13 (5.8) | 11 (8.9) | 0.2752 |
| Carotid Artery Stenosis | 38 (16.8) | 31 (27.0) | **0.0275** |
| Ipsilateral Carotid Artery Stenosis | 29 (76.3) | 24 (77.4) | 0.9140 |
| Cortical involvement on DWI, No. (%) | 123 (58.3) | 80 (69.6) | **0.0448** |
| Admission NIHSS, median (range) | 5 (0-34) | 12 (0-29) | **<0.0001** |
| IV tPA, No. (%) | 78 (32.8) | 49 (38.3) | 0.2911 |

Abbreviations: ND, neurological deterioration; LSN, last seen normal; ED, emergency department; TOAST, Trial of org 10172 in acute stroke treatment; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery; AICA, anterior inferior cerebellar artery; SCA, superior cerebellar artery; DWI, diffusion-weighted imaging; NIHSS, National Institutes of Health Stroke Scale score; IV tPA, intravenous tissue plasminogen activator.

## Table 4

Crude and adjusted associations of potential predictors for neurological deterioration during hospitalization.

| **Crude Associations** | **Odds Ratio** | **95%CI** | **P value** |
|---|---|---|---|
| Baseline NIHSS >14 | 2.95 | 1.83-4.75 | <0.0001 |
| Age >65 years | 2.20 | 1.41-3.43 | 0.0005 |
| Admission glucose >125 mg/dL | 1.63 | 1.06-2.52 | 0.0269 |
| ACA infarct | 3.63 | 1.31-10.07 | 0.0131 |
| Carotid stenosis >50% | 1.83 | 1.06-3.13 | 0.0288 |
| Coronary artery disease | 1.79 | 1.06-3.03 | 0.0294 |
| Adjusted Associations | Odds Ratio | 95% CI | P value |
| Age >65 years * | 1.78 | 1.11-2.93 | 0.0178 |
| Baseline NIHSS >14 ** | 2.64 | 1.56-4.49 | 0.0003 |

Abbreviations: CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale score; ACA, anterior cerebral artery.

* Adjusted for Baseline NIHSS >14, admission serum glucose level, carotid stenosis, and history of coronary artery disease.

** Adjusted for age >65, admission glucose, carotid stenosis, and history of coronary artery disease.

## Table 5

Combined odds of neurological deterioration according to age, baseline NIHSS, anterior cerebral artery infarct, and admission glucose level >125 mg/dL.

| | Age ≤65 years | Age >65 years |
|---|---|---|
| Baseline NIHSS 0-7 | 0.30 (0.15-0.60) **** | 0.34 (0.19-0.62) **** |
| +ACA infarct | 0.32 (0.156-0.648) *** | 0.35 (0.19-0.63) **** |
| +Admission glucose >125 mg/dL | 0.37 (0.16-0.67) *** | 0.36 (0.19-0.66) **** |
| Baseline NIHSS 8-14 | 1.40 (0.53-3.69) *NS* | 1.49 (0.76-2.95) *NS* |
| +ACA infarct | 1.52 (0.57-4.04) *NS* | 1.57 (0.79-3.12) *NS* |
| +Admission glucose >125 mg/dL | 1.52 (0.57-4.06) *NS* | 1.72 (0.85-3.47) *NS* |
| Baseline NIHSS >14 | 3.63 (1.69-7.79) **** | 2.42 (1.29-4.52) ** |
| +ACA infarct | 3.31 (1.51-7.26) *** | 2.29 (1.22-4.31) * |
| +Admission glucose >125 mg/dL | 3.18 (1.44-7.01) *** | 2.14 (1.12-4.09) * |

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; ACA, anterior cerebral artery.

The most significant factors associated with neurological deterioration, according to Table 4, were selected for further analysis in this model. Odds ratios for each group of baseline NIHSS reflect the odds of being admitted within that range of NIHSS scores in comparison to being admitted within the range of the other baseline NIHSS score groups. Additional combinations of risk factors (more than 3 at a time) could not be achieved due to sample size.

*NS* not significant (p>0.05)

* p<0.05

** p<0.01

*** p<0.005

**** p<0.001