Clinical Prediction of Functional Outcome After Ischemic Stroke
The Surprising Importance of Periventricular White Matter Disease and Race

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Background and Purpose—We sought to build models that address questions of interest to patients and families by predicting short- and long-term mortality and functional outcome after ischemic stroke, while allowing for risk reclassification as comorbid events accumulate.

Methods—A cohort of 451 ischemic stroke subjects in 1999 were interviewed during hospitalization, at 3 months, and at approximately 4 years. Medical records from the acute hospitalization were abstracted. All hospitalizations for 3 months poststroke were reviewed to ascertain medical and psychiatric comorbidities, which were categorized for analysis. Multivariable models were derived to predict mortality and functional outcome (modified Rankin Scale) at 3 months and 4 years. Comorbidities were included as modifiers of the 3-month models, and included in 4-year predictions.

Results—Poststroke medical and psychiatric comorbidities significantly increased short-term poststroke mortality and morbidity. Severe periventricular white matter disease (PVWMD) was significantly associated with poor functional outcome at 3 months, independent of other factors, such as diabetes and age; inclusion of this imaging variable eliminated other traditional risk factors often found in stroke outcomes models. Outcome at 3 months was a significant predictor of long-term mortality and functional outcome. Black race was a predictor of 4-year mortality.

Conclusions—We propose that predictive models for stroke outcome, as well as analysis of clinical trials, should include adjustment for comorbid conditions. The effects of PVWMD on short-term functional outcomes and black race on long-term mortality are findings that require confirmation. (Stroke. 2009;40:530-536.)

Key Words: ischemic stroke ■ outcomes ■ white matter disease ■ race ■ models ■ predicted models

One of the hardest questions asked at a stroke patient’s bedside in the acute care setting is “What is the prognosis?” This question can be reframed as a progressive series of questions. During the stroke hospitalization, the clinician is asked, “Will I die?” and “If I don’t die, will I be disabled?” After discharge from the acute hospitalization, eg, during outpatient follow-up, additional questions arise: “What is my long-term life expectancy?” and “Will my disabilities improve over time?”

Numerous predictive models exist. Some models for predicting short-term outcome are built on data that are available only during the acute hospitalization, with no adjustment made for subsequent comorbid events that may be relevant to poststroke outcomes. Other models take change over time into account with regard to poststroke recovery, but also do not account for subsequent events. Further, models for mortality and outcome in both the short and long term are rarely derived from longitudinal datasets with comprehensive measurements made at different time points.

We sought to demonstrate a method for developing predictive models that correspond to the pertinent questions asked by patients about both short- and long-term prognosis after ischemic stroke. We used data from a well-characterized cohort of patients who were assessed over a 4-year period after their strokes. Our aim was to test the feasibility of a practical approach where the model for predicting poststroke outcome changes over time, and which uses all data that are readily available at the particular points in time when questions about prognosis are asked. In our study, we collected data about poststroke medical and psychiatric comorbidities, some of which were due to stroke and others that were not. We hypothesized that 3-month outcomes are impacted by the occurrence of these comorbidities and that 4-year outcomes are impacted by 3-month outcomes. We present statistical models that use such a theoretical frame-
work, and we suggest that the questions asked in the clinical setting be used to drive outcomes research so that it is directly translatable to the clinical arena.

Methods

Subject Ascertainment and Short-Term Follow-Up
This work was undertaken as part of the Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS), a 5-county population-based study that tracks the regional incidence of stroke and case fatality. This study was approved by the Institutional Review Boards at all participating institutions, and detailed methods have been previously described.7–9

As part of Phase III of the GCNKSS, a cohort of ischemic stroke patients was prospectively identified from the larger stroke population. After a potential subject was identified as having had an ischemic stroke, the subject’s treating physician was contacted for permission to approach the patient for informed consent. Informed consent was obtained either from the patient, or from a proxy for patients who were unable to supply reliable information or were unresponsive, aphasic, or confused. (The order of preference for proxy was the spouse or live-in companion, adult child, parent, sibling, or close friend of the person.) All ischemic stroke patients during 1999 at any of the 17 hospitals in our study area were eligible for enrollment; the primary reason for not enrolling was discharge before contact for consent.

For each case, trained research nurses abstracted demographics, presenting symptoms, functional status before stroke, social, family, and medical histories, medications (including treatment with tPA as documented in the medical record), testing and laboratory results, and imaging studies. Data were recorded on case report forms. Stroke severity (retrospective NIH stroke scale score; NIHSS) was estimated from the medical record using the methods of Williams,10 which we have subsequently validated.11

Stroke team physicians reviewed each abstract and all available imaging studies to verify that each case was a stroke and to classify the subtype of stroke. Three-dimensional infarct volumes were measured using the modified ellipsoid method,12 and the degree of pertoventricular white matter changes was assessed using a 4-level ordinal scale (none, mild, moderate, or severe) similar to the methodology of Fazekas.13 When patients had multiple imaging studies, the first MRI scan was preferentially used for white matter grading.

This cohort was followed over time to determine both short-term functional outcome (assessed via an initial interview and a 3-month interview) and long-term functional outcome (assessed via interview at 4 years).

Initial Interview
Each consented patient or proxy underwent an initial face-to-face structured interview with a research nurse. The interview included questions about recent systemic illness, recent medications, past medical history, family history, and risk factors, including weight, eating behaviors, subjective stress ratings, and caffeine, alcohol, and tobacco use.

Three-Month Interview
At 3 months after stroke, research nurses telephoned patients or proxies and asked about vital status, poststroke hospitalizations, medical contacts other than simple office visits, and current residence. The modified Rankin Scale (mRS) and Barthel Index (BI) were used to determine the functional status of each surviving patient.

Assessment of Comorbidities
Research nurses retrospectively reviewed the hospital charts from the acute setting and all hospitalizations that had occurred in the 3-month poststroke period to document any new instance of an acute condition, new onset of a chronic condition, or exacerbation of a chronic condition, along with dates of occurrence. Thus, comorbidities were defined by documentation in the medical record. Case report forms were similar to those used by Johnston et al.4 Poststroke mRS was estimated at time of hospital discharge or at 30 days, if available. Because comorbidities were obtained retrospectively, it was not possible to determine whether a medical or psychological condition occurred as a direct result of the stroke. Comorbidities were classified by body system according to the National Cancer Institute’s Cancer Treatment Evaluation Program’s Common Terminology Criteria for Adverse Events, version 3 (http://ctep.cancer.gov/reporting/ctc.html); categories included neurological/neurovascular, cardiopulmonary, infectious, and psychiatric. In addition, we classified potentially fatal conditions as “life threatening.” Because data were collected retrospectively, we could not always determine whether a GI bleed, for example, was mild or life threatening. Thus, we treated any GI bleed as “life threatening.” We also collapsed comorbidities arising from cardiopulmonary, infectious, vascular (deep venous thrombosis), skin (decubitus ulcer), and other body systems into a “medical comorbidity” category. Groupings were not mutually exclusive—for example, a urinary tract infection was counted in both the “infectious” and “medical” categories. (A detailed description of the comorbidity categories appears in the supplemental Table I, available online at http://stroke.ahajournals.org.)

Four-Year Interview
Each surviving cohort member, or their proxy, was interviewed approximately 4 years poststroke. Functional outcomes were categorized using the mRS and BI. The patient or proxy was asked to recollect whether comorbidities had occurred.

Mortality
Mortality was assessed by use of Ohio and Kentucky death records (complete through 2003). The Social Security Death Index was searched via Rootsweb for deaths not already found in the Ohio and Kentucky records. Deaths found via chart review were verified by one or more of the three aforementioned sources.

Statistical Analysis
Logistic regression was used to predict the probability of death and linear regression was used to predict functional outcome at 3 months and 4 years. While we collected both mRS and BI functional outcome data, the mRS was our primary measure of functional status, and only mRS results are presented below. For modeling 3-month mortality and functional outcome, univariable analyses identified independent predictors from among clinically relevant variables that were reasonably available to physicians during the acute hospitalization after stroke admission, ie, demographics, medical history, acute imaging results, acute treatments, stroke severity scores (retrospective NIHSS), and measures of functional independence (mRS). Only these variables were considered in building the primary model for predicting 3-month outcomes. The effects of comorbidities that occurred during the 3-month period were considered separately, as modifiers of the predicted outcome. Although poststroke therapy (physical, occupational, and speech therapy) might also modify outcome, it was not included in the model because of its bidirectional effect; patients with excellent or poor poststroke status were both unlikely to receive therapy.

For modeling 4-year outcomes, variables available at baseline and in the short term (3 months after stroke) were considered, based on our theoretical framework that long-term survival and functional status are likely to be related to short-term recovery. Consideration of the variables available to the clinician at 3 months is akin to the questions patients ask at their 3-month follow-up visit regarding long-term prognosis. Significant predictors were then combined into a single model, and nonsignificant terms were removed using a manual backwards stepwise procedure.

For all modeling, collinearity of predictor variables was evaluated to minimize the likelihood of inappropriate inferences. At each stage of model development, the primary criterion for removal was a significance level less than 0.05. The impact of a variable’s removal was gauged by inspection of the regression parameter estimates to ensure that interactions and spurious relationships were not evident. In addition, because removing a variable based solely on significance level might result in a large change in model accuracy, nonsignificant variables were not removed if the C-statistic (for logistic
regression) or the $R^2$ (for linear regression) changed more than 0.1. Analyses were conducted using SPSS version 14.0 (SPSS Inc).

The functional outcome we modeled was the mRS, a 6-level ordinal variable. We elected to use linear regression for simplicity of interpreting our results. While using the mRS as a primary outcome variable in linear regression is inconsistent with the requirement that the dependent variable be continuous, the alternatives have significant disadvantages. Binary logistic regression would be simple to interpret, yet this would require dichotomization of the mRS at some arbitrary cut point. Appropriate selection of the cut point would be highly dependent on the individual concerns of the patient and the patient’s care-givers, and might variably be set as the point at which any disability is apparent (an mRS of 2 or above) or the point at which complete independence is lost (an mRS of 3 or greater). Considering a single binary cut point, therefore, does not satisfy our goal of answering the questions that patients might have. More appropriate would be multinomial logistic regression (or ordinal regression). With this approach, odds ratios are computed that indicate the effect of the predictor variable on the odds of having a certain mRS score compared to a reference mRS score. Odds ratios would be computed for each level of the mRS compared to the selected reference, which would result in a complex of parameter estimates. This would not satisfy our requirement of offering a straightforward explanation to patients of how they might fare following their stroke. Based on the assumption that the mRS is a coarse measure of an underlying continuous distribution of functionality, the underlying distribution is appropriately modeled using the linear regression technique.

Results
A cohort of 451 ischemic stroke patients agreed to participate in the longitudinal study. At baseline, there were 341 subject interviews and 110 proxy interviews. Functional outcome was measured for 406 of 415 surviving patients at 3 months, and for 154 of 301 surviving patients at 4 years. Figure 1 documents the inclusion and exclusion of patients in the samples used for the development of each predictive model. The characteristics of the 4 samples are given in Table 1. Because of the large number of patients excluded from the 4-year functional status model, these are also described in Table 1 to ascertain follow-up bias. Final multivariable models for functional outcome are presented in Tables 2 and 3 and for mortality in supplemental Tables II and III. (For each model, univariable analyses are presented in the appendix, including model-building steps.)

Three-Month Outcomes
The description of univariable and multivariable analyses for predicting mortality at 3 months is available online for mortality (Univariable, supplemental Table X; multivariable, supplemental Table V). When combined into a multivariable model, age and poststroke Rankin were significant independent predictors of 3-month mortality (supplemental Table II, model C-statistic 0.803, SE 0.038). Comorbidities, with the exception of psychiatric comorbidities, that occurred in the 3 months after stroke tended to increase the odds of 3-month mortality.

Among patients who survived to 3 months poststroke, univariable predictors of worse functional status included older age, not being partnered, not being a smoker, having diabetes, having a prior stroke, having PVWMD, having worse prestroke and poststroke functional status, greater stroke severity, and not being treated with thrombolitics. Additionally, male gender, white race, and increasing lesion volume had a tendency toward decreasing three-month functional status (supplemental Table IV). In multivariable modeling, age, diabetes, severe PVWMD, pre- and poststroke functional status, and stroke severity were related to 3-month mRS (Table 3, $R^2=0.484$). Medical, infectious, and neurovascular complications that occurred within the 3 months after stroke significantly worsened 3-month functional outcome. (Steps for the 3-month models are shown in supplemental Tables V and VI).

Long-Term Outcomes
The description of univariable (supplemental Table XI) and multivariable (supplemental Table VIII) analyses for predicting mortality at 3 months is available online. The final multivariable model (supplemental Table III) included age,
nonwhite race, and 3-month functional status as the primary predictors of 4-year mortality (C-statistic 0.740; SE 0.026).

Among patients who survived to 4 years, univariable predictors of worse functional status included older age at stroke, having diabetes, having had a prior stroke, poor functional status at prestroke, poststroke, and 3 months, greater stroke severity, and having psychiatric, infectious, or neurovascular comorbidities. Being treated with thrombolytics improved 4-year functional status. PVWMD and increased lesion volume tended to worsen functional outcome but were not significant (supplemental Table VII). In the final multivariable model (Table 3), functional status (prestroke, poststroke, and at 3 months), a history of a prior stroke, and the occurrence of infectious complications within 3 months after stroke all independently worsened 4-year mRS ($R^2$=0.508).

(Steps for the 4-year models are shown in supplemental Tables VIII (univariable) and IX (multivariable).)

**Discussion**

We have shown that statistical modeling driven by the clinical questions asked at different time points during a patient’s poststroke treatment and follow-up can be used to develop clinically useful models that are not static. Mortality and functional status outcomes benefit from different considerations, and in prognosticating long-term outcome, short-term recovery cannot be ignored. Our results suggest several unique findings. Our short-term model for functional outcomes reveals that severe PVWMD was associated with poor outcome. Furthermore, nonwhite race significantly predicts 4-year mortality. We are currently in the process of finalizing data collection on a similar cohort of patients to which we will apply our models to assess not only the feasibility of this practical way of thinking but also the validity of the models themselves. As such, we discuss here the hypotheses generated by our exploration and the potential impact of revising...
A 72-year-old man with diabetes and severe white matter disease, who has a prestroke mRS of 1, and an immediate poststroke mRS (upon hospitalization) of 3, with an NIHSS of 15. His initial predicted 3-month mRS from the model would be 3.5 (the constant of −0.33 is not shown).

He develops a urinary tract infection and depression. The urinary tract infection, in week 2 after the stroke, adds between 0.3 to 0.5 to his mRS. The depression is diagnosed at 4 weeks poststroke. This further adds 0.17 to his predicted 3-month mRS. Thus, his predicted mRS at 3 months would be estimated to be between 3.97 and 4.17.

Table 3. Final Multivariable Model Predicting 4-Year Functional Outcome (mRS), Including the Effect of Complications When Added to the Model

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>95% CI (β)</th>
<th>P</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.01</td>
<td>(0.00–0.02)</td>
<td>0.008</td>
<td></td>
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<tr>
<td>Diabetes</td>
<td>0.27</td>
<td>(0.02–0.51)</td>
<td>0.031</td>
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<tr>
<td>Severe PVWMD</td>
<td>0.47</td>
<td>(0.07–0.87)</td>
<td>0.021</td>
<td>0.484</td>
</tr>
<tr>
<td>Prestroke Rankin</td>
<td>0.20</td>
<td>(0.12–0.28)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Poststroke Rankin</td>
<td>0.56</td>
<td>(0.46–0.67)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Estimated NIHSS</td>
<td>0.03</td>
<td>(0.00–0.05)</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>Impact of complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life threatening</td>
<td>0.20</td>
<td>(−0.06–0.45)</td>
<td>0.127</td>
<td>0.488</td>
</tr>
<tr>
<td>complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical complications</td>
<td>0.31</td>
<td>(0.06–0.56)</td>
<td>0.014</td>
<td>0.494</td>
</tr>
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<td>Psychiatric complications</td>
<td>0.17</td>
<td>(−0.10–0.44)</td>
<td>0.211</td>
<td>0.487</td>
</tr>
<tr>
<td>Infectious complications</td>
<td>0.53</td>
<td>(0.27–0.79)</td>
<td>&lt;0.001</td>
<td>0.509</td>
</tr>
<tr>
<td>Cardiopulmonary</td>
<td>0.03</td>
<td>(−0.25–0.31)</td>
<td>0.821</td>
<td>0.484</td>
</tr>
<tr>
<td>complications</td>
<td>0.52</td>
<td>(0.17–0.88)</td>
<td>0.004</td>
<td>0.498</td>
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</tbody>
</table>

It should be noted that these models are not recommended for use in clinical settings at this time, as they have not been validated. However, an example is presented for ease of understanding the model construct.

With regard to the modeling, we feel that it is insufficient to look at one model that combines morbidity and mortality end points as they confound each other. Separating these outcomes is necessary for understanding which factors truly impact each end point, and our results suggest that different variables are relevant to each end point. Although this approach requires building 2 models for each time point, this process corresponds naturally to the clinical questions that patients and families will ask after a stroke has occurred. It is also best to consider how initial risk is modified by subsequent factors like treatment and comorbidities, which allows for progressive risk stratification as subsequent events occur in the poststroke setting. We have demonstrated that a range of comorbidities occurring in the post stroke setting, whether attributable to the stroke or not, impact mortality and the manner in which outcomes research in stroke is designed so that clinically practical questions are asked and answered.

Our results suggest several unique findings. Our short-term model for functional outcomes reveals that severe PVWMD was associated with poor outcome in our cohort. Previous work has shown that imaging findings such as stroke volume can significantly impact prediction of poststroke outcomes. Our results are consistent with this finding, with PVWMD independently associated with poor outcome in our model. This suggests that PVWMD is a significant predictor of poststroke outcome, and should be considered in future studies of poststroke recovery.

Figure 2. Theoretical model describing potential mechanisms altering functional outcome poststroke.

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Table 3. Final Multivariable Model Predicting 4-Year Functional Outcome (mRS)

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<tr>
<td>Prior stroke</td>
<td>0.58</td>
<td>(0.18–0.98)</td>
<td>0.005</td>
<td></td>
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<td>Prestroke Rankin</td>
<td>0.18</td>
<td>(0.02–0.34)</td>
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<tr>
<td>Poststroke Rankin</td>
<td>0.32</td>
<td>(0.15–0.48)</td>
<td>&lt;0.001</td>
<td>0.508</td>
</tr>
<tr>
<td>3-Month Rankin</td>
<td>0.29</td>
<td>(0.13–0.45)</td>
<td>0.001</td>
<td></td>
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<tr>
<td>Infectious complications</td>
<td>0.76</td>
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neurobiological factors. As such, traditional risk factors contribute to poor outcome by leading to increased PVWMD. Furthermore, PVWMD has been associated with higher incidence of cognitive decline and dementia, and those with greater incidence of cognitive decline will likely have less capacity for motor learning and functional recovery after stroke, leading to poor functional outcomes. The association of severe PVWMD with poor poststroke outcome must be explored in future studies, and more sophisticated quantitation of PVWMD burden should be undertaken. Figure 3 demonstrates that although some effect of lesser grades of PVWMD is evident, this does not impact on outcomes nearly as much as severe PVWMD. If severe PVWMD (or white matter disease burden above a more sophisticated quantitative threshold) is indeed proven to be associated with inability to recover after stroke, this will have important implications for future clinical trials studying stroke recovery. Inclusion of patients with severe PVWMD in a trial would potentially dilute the effect seen in the intervention arm if they are significantly less likely to recover. Alternatively, some therapies may be specifically targeted toward those patients with severe PVWMD who are otherwise unlikely or unable to recover. Interventions such as constraint induced therapy, epidural cortical stimulation, and others are already being tested to enhance poststroke recovery, and considering PVWMD as a modifier of the intervention might have significant implications particularly for studies that employ motor learning. The association between PVWMD and outcomes must be studied further to improve inclusion and exclusion criteria for future studies, thus allowing faster and more-cost efficient clinical trials to test recovery interventions. Finally, as PVWMD has been associated with cognitive decline, cognitive testing would be prudent in future recovery studies because motor learning may be impaired in those with highest PVWMD burden.

It is not surprising that outcomes at 3 months are highly significant predictors of outcomes at 4 years, although this approach is not commonly considered. It is surprising, however, that nonwhite race significantly predicts 4-year mortality. In our study, there were 2 Hispanic patients and 1 Asian patient in the nonwhite group, the remaining 146 were black. Thus, it might be concluded that this finding is driven by a difference between blacks and whites, although this may be a unique finding within the particular cohort being studied. Mortality data from the CDC have shown that stroke mortality is higher for blacks than whites, but we have shown in other studies that this is primarily because of higher stroke incidence in blacks as compared to whites. Previous analyses of long-term mortality in our population have not shown race to be a significant predictor of mortality at 30 days, 90 days, or 1 year, after adjusting for age. Some might interpret the effect of race presented here as a surrogate for the effects of socioeconomic status (SES), which we have previously shown to be related to stroke incidence. The current study did not include the collection of detailed socioeconomic data. We did capture insurance status, and, in an attempt to use this as a surrogate for SES, we included this among our predictor variables. However, in univariable models this was not found to be associated with outcomes. The finding that race may play a significant role in long-term poststroke mortality must be confirmed in subsequent studies and highlights the need to explore the interrelation of race, health culture, and SES, and their impact on long-term outcomes. Other factors could also be relevant such as racial differences in risk factor control or management of chronic diseases.

There were several findings that cannot be easily explained, such as the apparent beneficial effect of having smoked or having high cholesterol, which were found only in univariable analyses. This finding may be related to unique characteristics of the cohort willing to participate in the study both in the short and long term or survival bias. We collected a convenience sample of stroke patients, which is associated with survival bias and bias arising from early discharge, although other undetected biases might also occur. These biases are an expected component of our approach and modify our models to being applicable only to patients who survive the first few days after stroke and who remain hospitalized acutely. Testing and validation of the models are necessary, and this is currently underway. An-

![Figure 3. Relationship between periventricular white matter disease and functional outcome after stroke.](http://stroke.ahajournals.org/)}
other limitation of our models is nonuniform collection of poststroke mRS data (ranging from hospital discharge to 30 days poststroke). Comorbidities were retrospectively determined by documentation in the medical record, and there may be biases attributable to underdocumentation of some conditions, especially depression and anxiety. There was significant loss to follow-up between 3 months and 4 years, and the resulting biases shown in Table 1 may confound the results for long-term functional outcome. Available imaging review was often for CT scans, not MRIs. We did not consider “silent cerebral infarctions” (SCIs) for this analysis. In the dataset currently being assembled for testing our models, we will be able to investigate the impact of SCIs further. Finally, the overlap in categories of comorbidities makes use of models for prediction cumbersome, and further refinement of our methodology for handling these comorbidities is necessary.

In summary, we present an approach to modeling outcomes after stroke that is driven by the questions asked by patients and is relevant to the various time points when a clinician must attempt to answer them; this approach is also responsive to subsequent events that impact the outcomes. We contend that this is an improvement on traditional statistical modeling, and that incorporating such an approach in clinical trials as well as observational research will enhance the global adoption of new treatments, both acute and longer term, through improved contextualization of outcomes. In the course of our analyses, we have discovered several important relationships that warrant further investigation, including the associations of severe PVWMD with poor functional outcome, and of black race with long-term poststroke mortality.

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**Disclosures**

None.

**References**


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