Hypoalbuminemia Predicts Acute Stroke Mortality: Paul Coverdell Georgia Stroke Registry

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Background: Mortality remains unacceptably high among patients hospitalized for acute stroke. Additional knowledge about factors that contribute to mortality after stroke is important for instituting therapies to lower mortality. We sought to determine the factors that predict mortality in patients hospitalized for acute stroke.

Methods: In all, 1477 consecutively admitted patients with acute stroke in 34 hospitals in the state of Georgia participating in the Paul Coverdell Georgia Stroke Registry during a 3-month period (December 1, 2001-February 28, 2002) were identified by retrospective chart review using primary or secondary International Classification of Diseases, Ninth Revision codes. Of patients, 31% were black, 65% were white, and 58% were women. We determined inhospital mortality after admission for acute stroke in this representative group of patients.

Results: There were 154 (10%) inhospital deaths among the 1477 patients admitted with acute stroke. Univariate analysis showed that mortality was associated with older age (P = .0008), stroke type (P = .0051), Glasgow Coma Scale score less than 9 (P = .0001), decreased serum albumin (P = .0001), elevated creatinine (P = .0067), and elevated blood glucose (P = .0063). In the multivariate analysis, independent risk factors for mortality after acute stroke included older age (P = .004), stroke type (P = .0007), Glasgow Coma Scale score less than 9 (P = .0001), and decreased serum albumin (P = .0003). There was no relationship between race and inhospital mortality (P = .9041). In addition, there was no association between independent predictors and race.

Conclusion: In addition to previously recognized predictors of inhospital mortality, we found hypoalbuminemia to be an independent predictor of mortality in a biracial cohort of patients with acute stroke. Key Words: Acute stroke—mortality—risk factors—inhospital—hypoalbuminemia.

Stroke remains the third leading cause of death in the United States. Each year approximately 700,000 people in the United States are affected by stroke and on average someone dies of a stroke every 3 minutes. Estimates of inhospital mortality are 5% for acute ischemic strokes and 30% for acute hemorrhagic strokes. Other studies put estimates of inhospital mortality from stroke at 7% to 14%.

In general, early inhospital mortality from stroke is usually directly related to the stroke itself, whereas factors related to hospitalization and complications of being hospitalized influence death later in the course of acute stroke. Identifying factors that influence inhospital mortality from stroke may help in early identification of
patients at high risk and substantially decrease the number of avoidable deaths from acute stroke.

Previous studies have identified factors such as stroke severity, ischemic stroke subtype, hemorrhagic stroke, older age, impairment of consciousness, and hyperglycemia as predictors of mortality from acute stroke. However, these factors have varied depending on the population of patients being studied and may even differ between men and women among the same population of patients. Some studies have evaluated factors affecting inhospital mortality in a nonpopulation-based sample of patients from a single institution during a period of time or a small select group of patients from a single institution. We thereby sought to identify factors that influence stroke mortality among patients admitted for acute stroke in a representative sample of hospitals in the state of Georgia.

Methods

Hospital Selection

The Paul Coverdell Georgia Stroke Registry (PCGSR) was one of 4 sites initially funded by the Centers for Disease Control and Prevention in 2001 to design and implement a registry prototype. Hospital selection was intended to create a representative sample from the state. In Georgia, approximately one third of the hospitals were randomly selected using a simple random sampling procedure. The 8 largest hospitals in the state, in terms of stroke volume, were selected with certainty. Of the remaining hospitals, 52 hospitals were randomly selected using a random sort method. Of the selected hospitals, two thirds agreed to participate, yielding 34 registry hospitals in Georgia (Fig 1). Sampling weights were adjusted for nonparticipation, to help reduce the bias observed by including data from accommodating hospitals.

Data Collection

Data were collected retrospectively by identifying all patient charts after discharge during a 3-month period (December 1, 2001-February 28, 2002) with primary or secondary International Classification of Diseases, Ninth Revision codes (430, 431, 432.9, 433-436) and abstracted centrally by trained nurse abstractors at the state’s peer review organization—the Georgia Medical Care Foundation. Patients were included if acute stroke symptoms or signs were present on admission. Data collection included demographic and clinical variables suggested by an external expert panel and further developed and defined by the 4 state registry prototype sites (Georgia, Massachusetts, Michigan, and Ohio) and Centers for Disease Control and Prevention representatives.

Centrally abstracted information included age, sex, race, smoking status, atrial fibrillation on admission and coexisting disease (myocardial infarction, previous stroke, heart failure, hypertension, diabetes, and hyperlipidemia), first measured serum albumin, creatinine, hemoglobin, and blood glucose. Stroke type (ischemic, intracerebral hemorrhage [ICH], subarachnoid hemorrhage [SAH], or transient ischemic attack), initial Glasgow Coma Scale (GCS) score, and inhospital death were also ascertained. Serum albumin measurement was carried out according to standard methods in the different laboratories and the analyzed albumin level was the first measured serum albumin level recorded for each patient.

![STATE OF GEORGIA MAP](image)

**Figure 1.** Location of representative sample of hospitals across the state of Georgia that comprise PCGSR.
HYPOALBUMINEMIA PREDICTS ACUTE STROKE MORTALITY

Statistical Analysis

To adjust for the complex (stratified cluster) design and the variability in sampling weights (self-selected \& randomly selected hospitals), all tests of significance were performed using software (SUDAAN, Release 8.0, Research Triangle Institute, Research Triangle Park, NC). These tests include standard t tests for comparing means and percentages between mortality groups, Chi-squared tests for testing associations between mortality groups and discrete predictors, and logistic regression models for assessing complex associations. For the logistic regression models, all significant predictors from the exploratory analyses were included into the models, allowing assessment for confounding and interaction. Reported percentages are weighted to adjust for design and nonresponse. SUDAAN (Research Triangle Institute) produces appropriate weighted estimates, but also accounts for design effects in calculating standard error, which is not true for standard statistical packages.

For the PCGSR, case ascertainment was nearly complete (99%) based on monthly computerized discharge records from each hospital. For all variables collected, interrater agreement based on random replicate abstractions of charts between two trained abstractors was 87%.

Results

There were 1477 consecutively admitted patients identified with an acute cerebrovascular event meeting entry criteria from the 34 hospitals participating in the PCGSR across the state of Georgia (Fig 1). Frequency of stroke types were as follows: acute ischemic stroke (63%), transient ischemic attack (19%), ICH (9%), and SAH (3%). Of cases, 6% were classified as hemorrhages or strokes of undetermined type.

Patient Demographics

Of patients, 31% were black, 65% were white, 4% were of other ethnic groups, and 58% were women. There was no association between race and inhospital mortality ($P = .0041$) or between race and the independent predictors. There were 154 (10%) deaths during hospitalization.

Univariate Analysis

In the univariate analysis, factors such as age, stroke type, GCS score, elevated creatinine, decreased serum albumin, and elevated blood glucose distinguished survivors from nonsurvivors with regard to inhospital mortality after admission for acute stroke: age ($P = .0008$); stroke type ($P = .0051$); GCS score ($P < .0001$); albumin ($P = .0001$); creatinine ($P = .0067$); and blood glucose ($P = .0063$). The weighted means for these two groups are shown in Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fatalities</th>
<th>Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)*</td>
<td>73.60 ± 1.06</td>
<td>69.24 ± 0.75</td>
</tr>
<tr>
<td>GCS score*</td>
<td>8.70 ± 0.45</td>
<td>13.94 ± 0.13</td>
</tr>
<tr>
<td>Albumin (g/dl)*</td>
<td>3.39 ± 0.10</td>
<td>3.71 ± 0.05</td>
</tr>
<tr>
<td>Blood glucose (mg/dl)</td>
<td>161.53 ± 5.04</td>
<td>144.72 ± 3.20</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.49 ± 0.10</td>
<td>1.22 ± 0.06</td>
</tr>
</tbody>
</table>

Abbreviation: GCS, Glasgow Coma Scale.

*Independent predictors in multivariate logistic model.

Multivariate Analysis

In the multivariate logistic model, independent risk factors for mortality included age ($P = .004$), stroke type ($P = .0007$), GCS score ($P < .0001$), and serum albumin ($P = .0003$). These variables are summarized in Table 1 and depicted graphically for albumin in Fig 2.

Discussion

This analysis evaluated factors predicting inhospital mortality in a biracial cohort of patients admitted to a representative sample of hospitals in the state of Georgia, a region of the United States that is disproportionately affected by stroke.

In this group of patients, decreased serum albumin was an independent predictor of mortality in patients admitted for acute stroke. Older age and stroke type (ischemic hemorrhagic) were also independent predictors of mortality in the multivariate analysis. In addition, elevated creatinine distinguished survivors from nonsurvivors in the univariate analysis.

Hypoalbuminemia has not been widely evaluated as a predictor of mortality after acute stroke. In our cohort of patients, hypoalbuminemia (serum albumin < 3.4 g/dL) was independently associated with mortality in patients admitted for acute stroke.

Our study is one of the first to evaluate the role of hypoalbuminemia as a predictor of mortality in a racially diverse group of patients hospitalized for stroke. In a study evaluating predictors of short-term mortality in patients with stroke, hypoalbuminemia was found to be a predictor of mortality in older patients (median age 80 years) in the univariate analysis, but not in the multivariate analysis. Others have found hypoalbuminemia in hospitalized patients with acute stroke to be a strong independent predictor of mortality at 3 months after acute stroke. In addition, low albumin levels at the time of acute stroke seems to predict long-term mortality, up to 7 years, after the acute event.

Hypoalbuminemia may be an indirect marker of systemic conditions such as malnutrition and patients with low albumin levels may have other underlying chronic
medical or neurologic conditions that impair their ability to recover from acute stroke. Alternatively, low albumin levels at the time of acute stroke may simply be indicative of the role of albumin as a negative acute phase reactant whose concentration decreases during acute inflammatory states.24 A potential mechanism of hypoalbuminemia during acute inflammatory states, including acute stroke, involves negative regulation of albumin synthesis by interleukin (IL)-6 and tumor necrosis factor-α.25,26 Although not measured in our patients, both of these positive acute phase reactants, tumor necrosis factor-α and IL-6, have been found to be elevated during acute stroke.27 At the molecular level, some insight into the possible mechanism of IL-6 regulation of albumin synthesis emanates from the reversal of this IL-6-mediated effect on albumin synthesis by the peroxisome proliferator–activated receptor-α activator fenofibrate.29 In addition, hypoalbuminemia in acute stroke may be detrimental because low levels of serum albumin hamper some of albumin’s antioxidant30,31 and endothelial stabilization effects.32 It is not known whether reversing hypoalbuminemia or maintaining adequate albumin levels in patients with acute stroke will decrease mortality. An ongoing clinical trial of intravenous albumin may shed some light on the effect of treatment of patients with acute ischemic stroke.33

In addition to hypoalbuminemia, we also found that factors such as hyperglycemia, elevated creatinine (P = .0067), older age, stroke type (ischemic vs hemorrhagic), and type of intracranial hemorrhage (ICH vs SAH) distinguished those who survived from those who did not in our study. These findings are in concordance with previous studies that have shown the importance of these factors as predictive of mortality or increased morbidity from stroke.10-13,34-40

Our study was limited by its retrospective design with the potential for ascertainment or observational biases.41 However, in the PCGSR pilot program, case ascertainment was nearly complete at 99%. Also, we did not have adequate information on variables such as the National Institutes of Health Stroke Scale score, which might have shown the importance of these factors as predictive of mortality or increased morbidity from stroke.33

Another potential limitation was the presence of missing data. For example, albumin levels were available in most (72%), but not all patients. To further evaluate whether this may have introduced bias into the analysis, we analyzed the baseline characteristics of patients with

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Value range</th>
<th>Subjects/value range</th>
<th>Observed mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>&lt;50</td>
<td>180</td>
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<td>50-59</td>
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<td>70-79</td>
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<td></td>
<td>≥80</td>
<td>384</td>
<td>16</td>
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<td>GCS score</td>
<td>3-5</td>
<td>50</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>6-9</td>
<td>58</td>
<td>34</td>
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<tr>
<td></td>
<td>10-12</td>
<td>86</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>13-15</td>
<td>609</td>
<td>4</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&lt;2.0</td>
<td>8</td>
<td>63</td>
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<td>≥2.0-&lt;2.5</td>
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<td>≥2.5-&lt;3</td>
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<td>19</td>
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<tr>
<td></td>
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<td></td>
<td>≥3.5-&lt;4.0</td>
<td>403</td>
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<td></td>
<td>≥4.0</td>
<td>312</td>
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<td>Stroke type</td>
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<tr>
<td></td>
<td>TIA</td>
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<td></td>
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<td></td>
<td>SAH</td>
<td>43</td>
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</tr>
<tr>
<td></td>
<td>Other*</td>
<td>90</td>
<td>18</td>
</tr>
</tbody>
</table>

Abbreviations: AIS, acute ischemic stroke; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack.

*Hemorrhage or stroke of unknown type.

Patients older than 80 years had a mortality of 15.6% compared with 9.4% for patients younger than 50 years. With regard to stroke severity, patients with GCS score less than 9 had higher mortality compared with patients with higher GCS scores (≥9). In addition, as serum albumin levels decreased, acute stroke mortality increased. Patients with profound hypoalbuminemia had the greatest mortality: 62.5%.

Table 2. Mortality distribution by age, Glasgow Coma Scale score, serum albumin, and stroke type and the relationships between age, serum albumin levels, Glasgow Coma Scale score, and acute stroke mortality

Figure 2. With regard to albumin levels, patients with profound hypoalbuminemia (albumin < 2.0 g/dL) had mortality of 62.5% compared with mortality of 8.68% for well-nourished patients with albumin levels greater than 4.0 g/dL.
and without recorded albumin levels and found no differences with regard to inhospital mortality, stroke type, or demographic factors.

Conclusions

We report for the first time hypoalbuminemia as an independent predictor of mortality during hospitalization for acute stroke in a representative cohort of patients from a state located in the middle of the stroke belt. We propose that routine serum albumin measurement for determination of hypoalbuminemia be included in factors used early in hospitalization to stratify patients at high risk for inhospital mortality after acute stroke. Additional studies should be taken to determine whether correction of these factors leads to improved clinical outcome.

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References
