Cerebral Microbleeds are Associated with Higher Mortality Among Ischemic Stroke Patients

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Background: Several studies have shown that cerebral microbleeds (CMBs) increase the risk of long-term stroke-related mortality. The purpose of this study was to determine if the existence and burden of CMBs are a predictor of in-hospital death among patients with acute ischemic stroke (AIS). *Methods:* We studied consecutive ischemic stroke patients who admitted to our tertiary center over a 2-year period (2013-2014). Patients who underwent thrombolysis were excluded. Baseline characteristics of patients, number and topography of CMBs, white matter lesions, and spontaneous symptomatic hemorrhagic transformation were recorded. Outcome measure in our study was in-hospital death. *Results:* Out of 1126 consecutive AIS patients evaluated in this study, 772 patients included in the study (mean age 61.9 ± 14.2 years [18-95 years], 51.6% men, and 58.2% African American). CMBs were present on the magnetic resonance imaging (MRI) sequences of 124 (16.1%) patients. The overall rate of in-hospital mortality was 4.1%. The presence or absence of CMBs was not predictive of in-hospital mortality ($P = .058$). After adjusting for potential confounders, the presence of ≥4 CMBs on T2*-weighted MRI was independently ($P = .004$) associated with a higher likelihood of in-hospital death (odds ratio: 6.6, 95% confidential interval: 2.50 and 17.46) in multivariable logistic regression analyses. Older age, higher National Institute of Health stroke scale, and history of atrial fibrillation were also associated with greater chance of in-hospital death. *Conclusions:* The presence or absence of CMBs was not predictive of in-hospital mortality. However, the presence of multiple CMBs was associated with a higher in-hospital mortality rate among AIS patients.

Key Words: Cerebral microbleeds—in-hospital mortality rate—survival—acute ischemic stroke—prognosis

Introduction

Stroke remains the second leading cause of death worldwide.[1] More than 5% of the ischemic stroke patients experience in-hospital death,[2] Still, the reported incidence of stroke-related early mortality might be underestimated due to the exclusion of these patients in several studies.[3,4]

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Several factors such as age, stroke severity, impaired consciousness, the verbal component of the Glasgow Coma Scale, dependency to a ventilator, hyperglycemia, and fever are proposed as predictors of early mortality following acute ischemic stroke (AIS).[2,5-7] Among prognostic factors of in-hospital mortality, stroke severity (measured as National Institute of Health stroke scale [NIHSS]), history of atrial fibrillation, and plasma brain natriuretic peptide level are suggested as independent predictors.[2,8,9] Imaging parameters might also be valuable. Johnston et al demonstrated the potential of Diffusion-Weighted Imaging (DWI) lesion volume in clinical outcome prediction.[10]

Several studies have shown that cerebral microbleeds (CMBs) increase the risk of long-term stroke-related mortality.[11-14] It was also shown that the burden and location of CMBs could be associated with higher risk of death.[11,15-17] However, no previous study has reported in-hospital mortality rates among stroke patients with CMBs. The purpose of this study was to determine if the existence and burden of CMBs are a predictor of in-hospital death among patients with AIS.

Methods

Patient Selection and Baseline Records

We used the stroke database that we previously developed to study the racial difference in CMB burden among ischemic stroke patients. Inclusion criteria and details of data collection have previously been published.[18] In summary, the database included consecutive AIS patients presented to our tertiary care stroke center—University of Tennessee Health Science Center, Memphis, Tennessee, in a 2-year period (2013-2014). We excluded patients who received intravenous-tissue plasminogen activator.

Baseline characteristics of patients include age, gender, race, diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation, history of seizure disorder, history of stroke or transient ischemic attacks (TIAs), cigarette smoking, and clinical presentations. NIHSS was obtained per institutional protocol. We categorized spontaneous symptomatic hemorrhagic transformation (sHT) based on the classification of post-thrombolysis symptomatic intracerebral hemorrhage (ICH) defined by the European Cooperative Acute Stroke Study criteria combined with clinical deterioration of ≥4 points on NIHSS.[19] Outcome measure in our study was in-hospital death. This study was part of the University of Tennessee Health Science Center Acute Stroke Registry which had been approved by the university institutional review board.

Imaging Evaluation

The details of magnetic resonance imaging (MRI) evaluation have previously been published.[18] Briefly, all patients underwent a stroke brain MRI protocol—DWI, apparent diffusion coefficient, T2-fluid-attenuated inversion recovery, T2*-weighted gradient-echo and T1 weighted sequences. Head computed tomography (CT) was evaluated for the presence and burden of sHT according to European Cooperative Acute Stroke Study criteria.[19] Head CT with or without subsequent brain MRI was repeated in all patients who had worsening of neurological symptoms.

Statistical Analysis

Normal and skewed distributed continuous variables are presented as mean ± standard deviation and median (quartiles) respectively. Discrete values are demonstrated as median (quartiles). The statistical difference among groups was detected using the $\chi 2$ -test, Fisher's exact test, unpaired *t* test, and Mann-Whitney *U* test as indicated for dichotomous or continuous variables.

After determining the factors with significant correlation with in-hospital mortality, a multivariable logistic regression model was used to evaluate the prognostic factors affecting the in-hospital mortality and their effect size. To set an optimal threshold for the number of CMBs, we used receiver operating characteristic. Associations are presented as odds ratios with corresponding 95% confidence intervals (CIs). A P value of $<.05$ was considered as statistically significant. All analyses were performed by Statistical Package for Social Science (SPSS Inc, version 24 for Windows).

Results

A total of 1126 consecutive AIS patients were evaluated in this study. Three hundred fifty-four patients met our exclusion criteria (Table 1). Among patients who were excluded, 191 patients had received thrombolysis, and the rest did not have an MRI or an interpretable MRI. There was no significant difference among excluded and included patients in terms of age, gender, history of high blood pressure, diabetes, and previous stroke, the severity of stroke (NIHSS), in-hospital mortality rate, and modified Rankin Scale (mRS).

Among 772 included AIS patients (mean age 61.9 ± 14.2 years [18-95 years]; 51.6% men; 58.2% African American), 195 (25.2%) patients had a recurrent stroke (Table 1). The median admission NIHSS was 7 (interquartile range of 8). CMBs were present on the MRI sequences of 124 (16.1%) patients. The overall rate of in-hospital mortality was 4.1%.

The presence or absence of CMBs was not an indicator of in-hospital mortality ($P = .058$). However, the average number of CMBs was significantly higher among patients who died in the hospital (2.0 ± 4.2 versus .5 ±2.0; $P < .001$). Receiver operating characteristic curve indicated that the most optimal CMB threshold associated with in-hospital mortality was CMBs ≥4 (area under the curve