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Coagulation

Troponin elevation predicts critical care needs and in-hospital mortality after thrombolysis in white but not black stroke patients

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ABSTRACT

Introduction: Stroke patients undergoing intravenous thrombolysis (IVT) are at increased risk for critical care interventions and mortality. Cardiac troponin elevation is common in stroke patients; however, its prognostic significance is unclear. The present study evaluates troponin elevation as a predictor of critical care needs and mortality in post-IVT patients and describes racial differences in its predictive accuracy.
Methods: Logistic regression and receiver operating characteristics (ROC) analysis were used to determine racial differences in the predictive accuracy of troponin elevation for critical care needs and mortality in post-IVT patients.
Results: Troponin elevation predicted critical care needs in white (odds ratio [OR] 29.40, 95% confidence interval [CI] 4.86-177.81) but not black patients (OR 0.50, 95% CI 0.14-1.78; *P* value for interaction < .001). Adding troponin elevation to a prediction model for critical care needs in whites improved the area under the curve from 0.670 to 0.844 ($P = .006$); however, addition of troponin elevation did not improve the model in blacks (area under the curve 0.843 vs 0.851, $P = .54$). Troponin elevation was associated with in-hospital mortality in whites (OR 21.94, 95% CI 3.51-137.11) but not blacks (OR 1.10, 95% CI 0.19-6.32, *P* value for interaction .022).
Conclusion: Troponin is a useful predictor of poor outcome in white but not black post-IVT stroke patients.

1. Introduction

Intravenous thrombolysis with recombinant tissue plasminogen activator (IVT) is the only approved therapy for acute ischemic stroke and is currently the cornerstone of therapy for patients presenting within 4.5 hours of symptom onset [1]. Stroke patients undergoing IVT are at increased risk for needing critical care interventions due to sequelae of their underlying stroke as well as IVT-related complications. Post-IVT patients are monitored either in an intensive care unit (ICU) or a stroke unit [2]; however, no evidence-based triaging standards exist, and triaging criteria for monitoring intensity and environment vary by institution. Because only approximately 30% of post-IVT patients require critical care resources [3], identification of a priori factors predicting need for critical care interventions is needed.

Markers of myocardial injury, such as cardiac troponin I, are elevated in up to 30% of all stroke patients [4,5]. The etiology of elevated serum troponin in acute stroke patients is unclear but may be related to increased cardiac strain in the setting of acute hypertension, may be caused by true thrombotic coronary ischemia, may reflect concomitant atrial fibrillation or congestive heart failure as the underlying stroke etiology, or may be related to myocardial damage in the setting of sympathoadrenal activation [6,7]. The prognostic significance of troponin elevation is unclear, and whether troponin elevation is associated with poor outcome and mortality remains controversial [4,8]. Aforementioned studies investigating the predictive value of serum troponin in stroke patients were carried out in mainly white European populations, with underrepresentation of black patients. Black stroke patients may differ from their white counterparts with regard to underlying stroke etiology and risk factor profile; that is, atrial fibrillation is more common in white compared with black stroke patients [9,10], whereas blacks more commonly present with refractory hypertension [11]. These racial differences might extend to differences in other clinical features on presentation, including troponinemia.

The present study aimed to determine the significance of troponin elevation as a predictor of critical care needs and mortality in stroke patients undergoing IVT and explore the predictive value of troponin elevation differentially by race. We tested the hypothesis that troponin elevation is an important and valuable predictor of need for ICU level of care in whites but not blacks. To our knowledge, this is the first

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study to explore racial differences in predictors of critical care needs after IVT to develop tailored prediction models.

2. Methods

2.1. Patients and study design

This study was approved by the Johns Hopkins University School of Medicine Institutional Review Board. A waiver of consent was granted based on 45 CFR 46.116. An Institutional Review Board waiver of HIPAA privacy authorization was also granted to allow review of medical records to abstract data to deidentify for use in research. Patients who were treated with IVT for acute ischemic stroke in the emergency department at Johns Hopkins Hospital and Johns Hopkins Bayview Medical Center, per standard protocol, between January 2010 and December 2014 were identified from our prospectively collected stroke database.

Demographic data including age, sex, and race were collected for all patients. Other variables of interest, obtained from the medical records, included stroke risk factors: hypertension; hyperlipidemia; diabetes mellitus; smoking status; history of atrial fibrillation; history of coronary artery disease (CAD); prior history of stroke; and the prehospital use of antiplatelet agents, anticoagulation, and statins. National Institutes of Health Stroke Scale (NIHSS) and the following physiologic parameters at presentation were recorded: blood pressure (BP), serum glucose, serum creatinine, glomerular filtration rate (GFR), and elevated troponin upon admission defined as a serum troponin I greatear than 0.06 ng/ml within the first 6 hours of presentation. Decisions about whether troponin should be checked on an individual patient are made by the teams caring for the patient in the emergency department and on the neurology service, but it is standard for most patients undergoing IVT to get a troponin level checked on admission (pre-IVT). Data on total length of stay (LOS), length of ICU stay, discharge destination, withdrawal of care, and in-hospital mortality were collected. The presence of any critical care intervention was recorded while blinded to the troponin status of each patient. A critical care intervention was considered any therapy or intervention that required ICU resources as defined previously [3]. Specifically, ICU admission criteria included uncontrolled hypertension requiring titration of IV antihypertensives, use of vasopressors either for symptomatic systemic hypotension or blood pressure augmentation, need for invasive hemodynamic monitoring, uncontrolled hyperglycemia requiring IV insulin, respiratory compromise resulting in either initiation of bilevel positive airway pressure or mechanical ventilation, anaphylaxis, arterial bleeding, management of cerebral edema and increased ICP, neurosurgical intervention such as decompressive craniectomy, or symptomatic intracerebral hemorrhage (sICH) defined as any ICH with neurological deterioration, as indicated by a change in NIHSS greater than or equal to 4 compared with the baseline as described previously [12]. Our definition of an ICU intervention also included ICU monitoring, as for patients with any event or complication that would require monitoring in an ICU setting even if no immediate ICU intervention was performed, such as progressive decrease in mental status with impaired airway protection, increasing oxygen requirement, or detection of potentially life-threatening arrhythmia.

2.2. IV thrombolysis protocol

At our institutions, IVT is administered according to the American Heart Association's national guidelines [2]. Post-IVT monitoring conforms to the recommendations of the Brain Attack Coalition, which have become the standard of care for most stroke centers. All patients receiving IVT are monitored in the neurointensive care unit for at least 24 hours after initiation of thrombolysis, and undergo neuroimaging with either computed tomography or magnetic resonance imaging within 24 hours after treatment before being considered for transfer to the floor.

2.3. Statistical analysis

Statistical analysis was performed using Stata version 13 (Stata Statistical Software: Release 13, College Station, TX). A 2-sided P value of $< .05$ was considered statistically significant, and 95% confidence intervals (CIs) are reported. For univariate analyses, continuous variables were analyzed using Student t tests for normally distributed variables and Wilcoxon rank sum tests (Mann-Whitney U test) for nonnormally distributed variables. Categorical variables were analyzed using Pearson χ^2 analysis and Fisher exact tests when appropriate.

The primary outcome of interest was need for ICU intervention, and in-hospital mortality was the secondary outcome. Serum troponin elevation on admission was the primary predictor of interest. Simple logistic regression was used to determine univariate associations of troponin elevation and need for critical care interventions by race. Multivariable logistic regression was performed adjusting for basic demographic variables as well as other variables previously published to be associated with ICU needs or felt to be potentially clinically relevant for predicting critical care interventions, such as NIHSS, systolic BP (SBP), and serum glucose. Because in-hospital mortality as our secondary outcome is a relatively rare event, we used logistic regression with Firth's penalized likelihood for analyses with mortality as the outcome of interest [13].

For prediction models, we used Akaike information criterion for model selection. The discriminative ability of the area under the receiver operating characteristics (ROC) curves of the final models with and without troponin were compared by using a nonparametric approach described by DeLong et al [14]. Model calibration was assessed with the Hosmer-Lemeshow test to determine goodness of fit, and the final prediction models were validated by leave-one-out cross-validation.

Troponin values were missing in about 30% of patients. To ensure that missingness of troponin values did not influence our findings by introducing selection bias, we compared baseline characteristics of patients with missing and nonmissing troponin values. We then used multiple imputation by chained equations with 30 iterations to impute missing troponin values for 86 patients. We repeated the primary analysis with the imputed data sets, and the troponin values were averaged across the 30 imputed data sets [15].

3. Results

3.1. Patient selection and characteristics

Three hundred and one patients received IVT for acute ischemic stroke at our institutions between January 2010 and December 2014. Nine nonwhite, nonblack patients were excluded. Of the remaining 292 patients, troponin measurements were available in 206 (70.5%), constituting the primary study population. There were no differences in the frequency of troponin collection by race (50.5% of patients with troponin were black, whereas 47.7% of patients without troponin were black; $P = .66$). Compared with patients without measured troponin, patients with troponin were more likely to be male (53.4% vs 40.7%, $P = .048$), had higher NIHSS at presentation (median 8 vs 6, $P = .003$), and were more likely to have a history of atrial fibrillation (24.8% vs11.6%). Baseline characteristic of patients with missing troponin values not included in the primary analysis can be found as Supplemental Table 1.

We compared baseline characteristics of blacks (104; 50.5%) with whites (102; 49.5%). Blacks were more likely to present at a younger age (median 60 years vs 70 years, $P < .002$) and had higher diastolic blood pressure compared with whites (median 95 vs 87 mm Hg, $P = .001$). White patients more commonly presented with a history of hyperlipidemia (59.8% vs 43.3%, $P = .018$) and CAD (35.3% vs 19.2%, $P = .010$). Serum troponin levels were elevated in 16.4% of black and 9.8%