Predictors of Systemic Inflammatory Response Syndrome in Ischemic Stroke Undergoing Systemic Thrombolysis with Intravenous Tissue Plasminogen Activator

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Background: Systemic inflammatory response syndrome (SIRS) is an inflammatory process associated with poor outcomes in acute ischemic stroke (AIS) patients. However, no study to date has investigated predictors of SIRS in AIS patients treated with intravenous (IV) tissue plasminogen activator (tPA). *Methods:* Consecutive patients were retrospectively reviewed for evidence of SIRS during their acute hospitalization. SIRS was defined as the presence of 2 or more of the following: (1) body temperature less than 36°C or greater than 38°C, (2) heart rate greater than 90, (3) respiratory rate greater than 20, or (4) white blood cell count less than 4000/mm or greater than 12,000/mm or more than 10% bands for more than 24 hours. Those diagnosed with an infection were excluded. A scoring system was created to predict SIRS based on patient characteristics available at the time of admission. Logistic regression was used to evaluate potential predictors of SIRS using a sensitivity cutoff of ≥65% or area under the curve of .6 or more. *Results:* Of 212 patients, 44 had evidence of SIRS (21%). Patients with SIRS were more likely to be black (61% versus 54%; $P = .011$), have lower median total cholesterol at baseline (143 versus 167 mg/dL; $P = .0207$), and have history of previous stroke (51% versus 35%; $P = .0810$). Ranging from 0 to 6, the SIRS prediction score consists of African American (2 points), history of hypertension (1 point), history of previous stroke (1 point), and admission total cholesterol less than 200 (2 points). Patients with an SIRS score of 4 or more were 3 times as likely to develop SIRS when compared with patients with a score of ≤3 (odds ratio = 2.815, 95% confidence interval

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1.43-5.56, $P = .0029$). *Conclusions:* In our sample of IV tPA-treated AIS patients, clinical and laboratory characteristics available on presentation were able to identify patients likely to develop SIRS during their acute hospitalization. Validation is required in other populations. If validated, this score could assist providers in predicting who will develop SIRS after treatment with IV tPA. **Key Words:** Thrombolysis—systemic inflammatory response syndrome—stroke outcome—inflammation.

Introduction

Systemic inflammatory response syndrome (SIRS) is an inflammatory process in the absence of infection that is characterized by 2 of the following: body temperature changes (<36°C or >38°C), leukocytosis or leukopenia, elevated heart rate, or elevated respiratory rate.[1] Inflammation plays a role in the pathophysiology of tissue damage through ischemia–reperfusion injury.[2-5] Audebert et al[6] showed that inflammatory reactions after stroke result from the activation of cellular, humoral, and metabolic mechanisms, which can lead to an increase in necrotic tissue in the ischemic penumbra.

Similar to increased body temperature, leukocytosis is independently associated with poor functional outcome in acute stroke patients.[7,8] Previous research has shown that acute ischemic stroke (AIS) patients with more severe strokes are at higher odds of having SIRS but that successful thrombolytic therapy attenuates this process.[6] A study of tissue plasminogen activator (tPA)–treated patients illustrated how SIRS is associated with poor short-term functional outcome and increased length of hospital stay.[9]

We aimed to identify predictors of SIRS in patients with acute ischemic stroke who were treated with tPA and, subsequently, develop a prediction score to aide clinicians in assessing which stroke patients are at risk for SIRS development.

Methods

Study Population and Variable Definition

Consecutive patients presenting with acute ischemic stroke to a single academic center from 2009 to 2011 who were treated with intravenous (IV) tPA were identified using an existing prospective stroke registry. Admission demographic and clinical data and outcome measures were extracted. Clinical characteristics included vital signs, physical exam findings, stroke severity (as measured by the National Institutes of Health Stroke Scale [NIHSS]), and laboratory and imaging results. Retrospective chart review was used to identify patients who developed SIRS during their hospital stay. SIRS was defined as the presence of 2 or more of the following: (1) body temperature less than 36°C or greater than 38°C, (2) heart rate greater than 90, (3) respiratory rate greater than 20, or (4) white blood cell count less than 4000/mm or greater than 12, 000/mm or more than 10% bands for more than 24 hours. Patients who were diagnosed with an infection were excluded because the focus of the study was an uninfected inflammatory response after acute ischemic stroke, not sepsis.[1,10]

The outcome of interest was the presence of SIRS during the acute hospitalization period. We compared admission, clinical, and discharge information between patients who developed SIRS and patients who did not develop SIRS. This information was used to determine which features were predictive of a patient developing SIRS.

Statistics

Demographic and clinical data during the inpatient stay was compared across patients with SIRS and those without SIRS using chi-square and t tests, with nonparametric equivalents when appropriate. A prediction model was designed to estimate which patients would develop SIRS. The prediction models were built using a random sample of 55% of the data set (build group) and subsequently tested on the remaining random 45% (test group). Additionally, the scores were tested on the entire population after score development. All available demographic, clinical, and laboratory variables available at the time of admission were examined, using logistic regression models where development of SIRS was equal to 1. Variables with P values of .2 or less were retained in the final model. ROC curves were used to evaluate continuous variables. In addition, sensitivities were calculated to investigate grouping continuous variables. After the variables were assessed individually using the .2 or less cut point for the P value, we then placed variables that met this requirement in the multivariable model. The points assigned to the variables in the score were determined using the beta coefficients from the final multivariable logistic regression model. Once in the multivariable model, we then maximized the area under the curve (AUC) of the ROC curve by weighting variables from the multivariable models in an effort to develop the most predictive scoring algorithm. Spearman correlation and ROC curves were used to evaluate the final score. Additional logistic regression analyses were used to test the SIRS prediction score