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

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Abstract

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

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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 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.

Keywords

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 as a predictor of those with 2 SIRS components, those with 3 SIRS components, and those with 4 SIRS components. As this was an exploratory analysis, no adjustments were made for multiple comparisons.[11] An alpha of .05 was set as the level of significance.

Results

Baseline Results and Prevalence of SIRS

In the 241 IV tPA-treated patients who met study inclusion criteria, there were 44 who had evidence of SIRS (18.2%). The median age of the 241 participants was 63 (range 20–99), with 107 females (44%), and a median admission NIHSS score of 7 (range 0–32). Table 1 demonstrates the differences in baseline characteristics between patients who developed SIRS during their inpatient stay and patients who did not develop SIRS. Patients with SIRS were more likely to be black (48% versus 25%; $P = .0117$), had lower median total cholesterol at baseline (143 versus 168 mg/dL; $P = .0207$), and more frequently reported a history of previous stroke (52% versus 35%; $P = .0810$) and hypertension (82% versus 70%, $P = .1019$). In the unadjusted models, black race (odds ratio [OR] = 2.7, 95% confidence interval [CI] 1.37–5.26, $P = .0040$) was a significant independent predictor of SIRS, whereas previous stroke (OR = 1.98, 95% CI .91–4.29, $P = .0839$) and history of hypertension (OR = 1.97, 95% CI .86–4.49, $P = .1066$) failed to be significant independent predictors of SIRS. When divided into 3 categories (0–7, 8–14, and >14),[12] admission stroke severity was not found to be a significant independent predictor of SIRS (OR = 1.19, 95% CI .79–1.81, $P = .3898$). The SIRS frequency data and patient characteristics were further used to develop a score to aid prediction of which patients would develop SIRS. Of those with SIRS, 4 patients had 4 of the SIRS components, 14 patients had 3 of the SIRS components, and 26 patients had 2 of the SIRS components. Table 2 shows the breakdown of SIRS components for each of these SIRS categories.

SIRS Prediction Score

Black race, total cholesterol, history of hypertension, history of previous stroke, on nicardipine, and history of heart failure met the <.2 univariable *P* value cutoff (Table 3). The variables such as treatment with nicardipine and heart failure were not included in the final prediction model because of low predictive value as measured by AUC of the ROC (.5550 and .5464, respectively). The cutoff for total cholesterol was determined by testing different cut points in the final multivariable model to assess which cutoff was more predictive through the total model AUC.

The final score allotted 2 points for black race, 2 points for total cholesterol being lower than 200, 1 point for history of hypertension, and 1 point for history of previous stroke. The SIRS prediction score ranged from 0 to 6 (Table 4) and produced an AUC of .7430 (Fig 1). Using the entire cohort, 80% of patients with an SIRS prediction score of 4 or more developed SIRS. Figure 2 illustrates the distribution of the SIRS prediction score compared with patients who develop SIRS. Additionally, the odds of a patient with an SIRS prediction score of 4 or more developing SIRS was nearly 3 times that of patients with SIRS prediction scores of 0–3 (OR = 2.82, 95% CI 1.43–5.56, $P = .0029$). Figure 3 illustrates the distribution of the SIRS prediction score stratified by those with 2, 3, and 4 SIRS components.

Discussion

Our study showed that a novel predictive score can identify patients who are at 3-fold higher odds to develop SIRS after ischemic stroke and treatment with tPA. To our knowledge, this is the first study to investigate the predictors of SIRS in tPA-treated acute ischemic stroke patients using the definition and diagnostic workup that rules out sepsis and infection during the hospital stay. Using information available at the time of admission, we developed an SIRS prediction score for tPA-treated ischemic stroke patients. The SIRS prediction score is a simple, easy to use score that can provide clinicians with the probability that a tPA-treated patient will develop SIRS. It is highly predictive in those with 2 and 3 of the SIRS components, and it is technically predictive in those with 4 of SIRS components, but the total number of those with 4 SIRS components is very small and the predictive ability could be stronger in a larger sample size. We acknowledge that by setting the SIRS prediction score threshold relatively high (ie, 4), some patients with low SIRS prediction scores (and possibly a milder form of SIRS) will be missed.

Little research has been done on SIRS in acute ischemic stroke patients, but despite this, the specific components of the SIRS prediction score are comparable with work done in inflammation in stroke and SIRS in other conditions. The finding of history of previous stroke as a significant predictor of SIRS could be a function of stroke severity and greater overall risk factor burden before stroke recurrence. Audebert et al[6] showed that patients with higher admission NIHSS were more likely to experience SIRS. Work performed by Dhar et al[13] in subarachnoid hemorrhage patients showed that patients with SIRS were more likely to have a history of hypertension than those without SIRS (50% versus 34%). Furthermore, lower total cholesterol has been shown to be associated with critical illness and correlated with increased concentrations of cytokines.[14–17] Bonville et al[18] found that decreased serum cholesterol is an independent predictor of mortality in SIRS patients. The frequency of SIRS in AIS could be a function of chronic disease burden. Wang et al[19,20] found that incident sepsis episodes were associated with older age, dyslipidemia, hypertension, atrial fibrillation, stroke and peripheral artery disease to name a few, and the risk of sepsis increases with the number of chronic medical conditions. Interestingly, previous research has shown that black trauma victims have lower rates of SIRS than whites and lower rates of sepsis as well.[19,21] The finding that black patients have higher rates of SIRS may be a function of the chronic disease burden seen in blacks.

Our study is limited by the retrospective nature and small sample size involving only 1 academic center. We also are only examining AIS patients treated with IV tPA. Validation in additional cohorts is needed to determine the generalizability of our SIRS prediction score to AIS patients in general and other patient populations. Additionally, we did not have inflammation biomarkers. Despite our limitations, this is the first study to develop an SIRS prediction score for tPA-treated acute ischemic stroke patients.

Conclusions

This study provides a scoring system that predicts the development of SIRS in tPA-treated patients, using information available at the time of admission. SIRS is an important clinical

event that affects prognosis. Prospective studies with a larger sample size are needed to determine if early identification of patients at risk for SIRS, followed by swift treatment for those who develop SIRS, can decrease the risk of poor functional outcome in this susceptible group.

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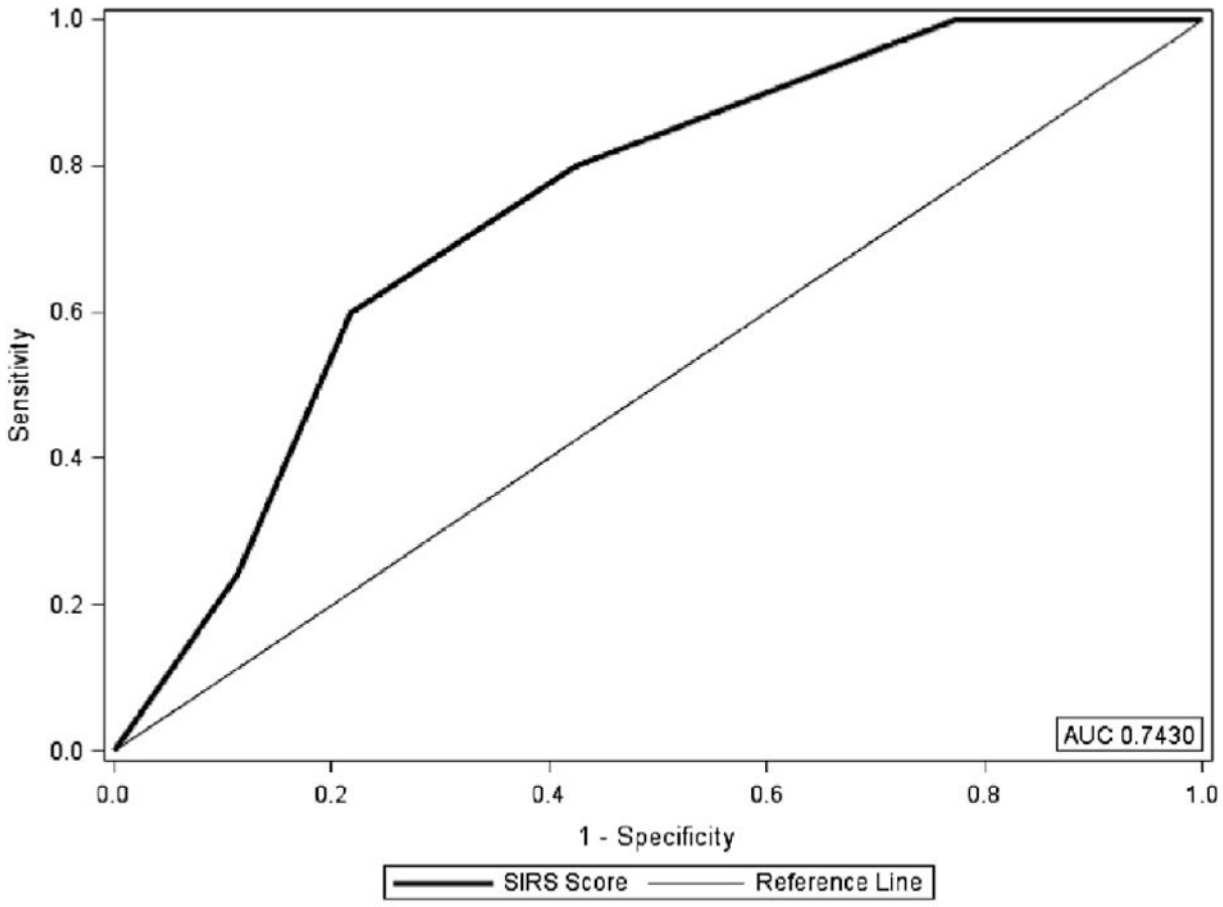

Figure 1.
SIRS prediction score as a predictor for SIRS. Abbreviation: SIRS, systemic inflammatory response syndrome.

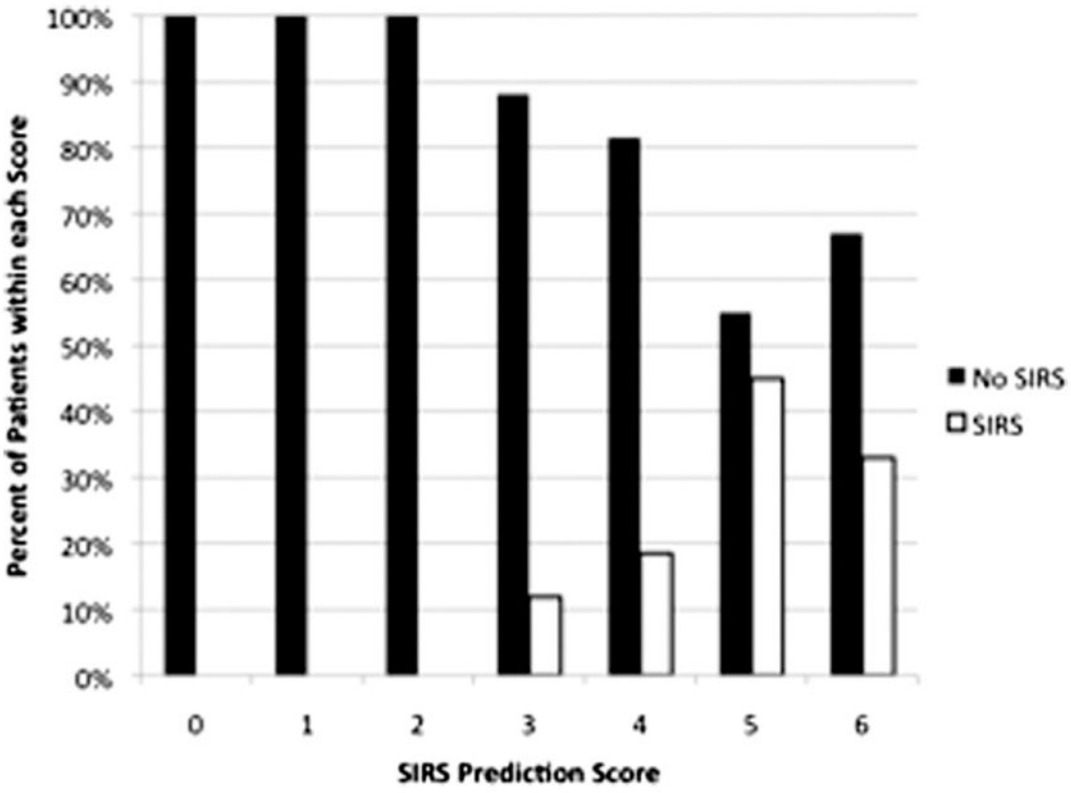

Figure 2.
Distribution of patients with SIRS based on SIRS prediction score. Abbreviation: SIRS, systemic inflammatory response syndrome.

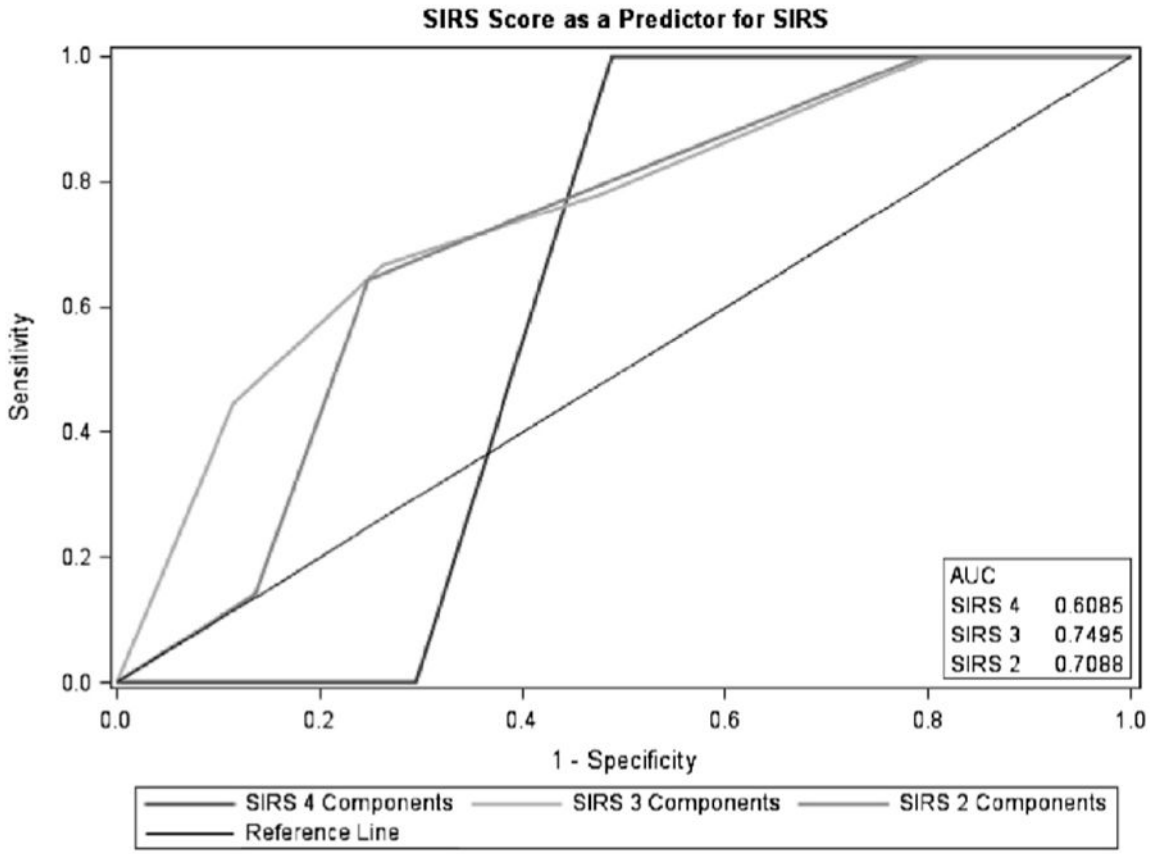

Figure 3.

SIRS prediction score as a predictor for SIRS stratified by number of SIRS components.

Abbreviation: SIRS, systemic inflammatory response syndrome.

Table 1

Baseline characteristics of patients with SIRS compared to patients without SIRS

	No SIRS (N = 197)	SIRS (N = 44)	*P* value
Age	63 (20–99)	64 (21–96)	.7704
Gender, % male	107 (54.3%)	27 (61.4%)	.3949
Black race	50 (25.4%)	21 (47.7%)	.0117
Medical history, %			
Stroke	44 (34.9%)	17 (51.5%)	.0810
Atrial fibrillation	30 (15.2%)	8 (18.2%)	.6270
Diabetes	49 (24.9%)	9 (20.5%)	.5353
Hypertension	137 (69.5%)	36 (81.8%)	.1019
Dyslipidemia	67 (34.0%)	13 (29.6%)	.5696
Heart failure	22 (11.2%)	9 (20.5%)	.0962
ESRD/CKD	10 (5.1%)	3 (6.8%)	.6437
Active smoker	54 (27.4%)	11 (25%)	.7446
On BP meds at home	112 (56.8%)	26 (59.1%)	.7861
On DM meds at home	32 (16.2%)	7 (15.9%)	.9566
On AP meds at home	69 (35.0%)	18 (40.9%)	.4625
Transfer	71 (36.0%)	11 (25%)	.1623
NIHSS on admission	7 (0–31)	9 (0–32)	.1015
Length of stay	3 (0–52)	5 (1–41)	<.0001
Glucose	111 (73–536)	114 (65–450)	.4761
PT	14 (11–36)	14 (13–20)	.0043
INR	1.07 (.83–3.48)	1.11 (.96–1.63)	.0088
PTT	28 (19–63)	27.5 (20–52)	.7848
HCT	40 (15–89)	38 (27–50)	.1200
RBC	4.4 (2.1–15.1)	4.2 (2.4–12.6)	.1169
A1C	5.8 (4.8–16.5)	5.7 (4.9–12.2)	.6143
Total cholesterol	167.5 (60–439)	143.5 (88–245)	.0207
Transfusion	2 (1.0%)	1 (2.3%)	.3687
Follow-up imaging	164 (83.3%)	39 (88.6%)	.3753
Hemorrhagic transformation	17 (8.6%)	4 (9.3%)	.8875
SIRS criteria			
Temperature	0	16 (36.4%)	
RR	0	37 (84.1%)	
HR	0	37 (84.1%)	
WBC	0	20 (45.5%)	
On Nicardipine	15 (7.6%)	8 (18.6%)	.0265
mRS on admission	0 (0–5)	0 (0–4)	.1486
mRS on discharge	3 (0–6)	4 (1–6)	.0003
mRS score 0–2 on discharge	92 (48.2%)	9 (20.9%)	.0011
Favorable discharge disposition	146 (76.4 %)	31 (73.8%)	.7180

	No SIRS (N = 197)	SIRS (N = 44)	*P* value
Death	21 (10.7%)	8 (18.2%)	.1656

Abbreviations: AP, antiplatelet; BP, blood pressure; DM, diabetes mellitus; HCT, hematocrit; HR, heart rate; INR, international normalized ratio; meds, medications; NIHSS, National Institutes of Health Stroke Scale; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell; RR, respiratory rate; SIRS, systemic inflammatory response syndrome; WBC, white blood cell.

Table 2

Proportion of each SIRS criteria seen in patients with 2, 3, and 4 SIRS criteria

	SIRS 4 (N = 4)	SIRS 3 (N = 14)	SIRS 2 (N = 26)	*P* value
Heart rate>90	4 (100%)	13 (92.8%)	20 (76.9%)	.0841
Respiratory rate > 20	4 (100%)	12 (85.7%)	21 (80.8%)	.1562
Temperature < 36°C or >38°C	4 (100%)	9 (64.3%)	3 (11.5%)	<.0001
White blood cells < 4000/mm or >12,000/mm or >10% bands for >24 h	4 (100%)	8 (57.1%)	8 (30.8%)	.0027

Table 3

Variables included in the prediction model

	Sensitivity/specificity or area under the curve	Univariable *P* value	Univariable beta coefficient (SE)
Black race	47.8/74.6	.0040	.987 (.34)
Hypertension	81.8/30.5	.1066	.6784 (.42)
Total cholesterol	.6238	.0328	−.01 (.004)
History of previous stroke	51.5/65.1	.0839	−.34 (.20)
Heart failure	20.4/88.8	.1014	.7156 (.44)
On Nicardipine	18.6/92.4	.0318	1.02 (.48)
PT	.6349	.4243	.0560 (.06)
INR	.6294	.4442	.4929 (.64)

Abbreviations: INR, international normalized ratio; PT, prothrombin time.

Table 4

SIRS prediction score (0–6 points)

Race	**Total cholesterol**
Black/African American = 2 points	<200 = 2 points
Other race = 0 point	≥200 = 0 point
Hypertension	**History of previous stroke**
Hypertension = 1 point	History of previous stroke = 1
No hypertension = 0 point	No evidence = 0 point