

Systemic Inflammatory Response Syndrome and Outcomes in Ischemic Patients Treated with Endovascular Treatment

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Research

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Abstract

Background The occurrence of systemic inflammatory response syndrome (SIRS) is associated with poor outcomes after ischemic stroke, and the inflammatory response can be significantly attenuated by successful reperfusion, while the SIRS in patients with acute large vessel occlusion stroke (ALVOS) who underwent endovascular treatment (EVT) remain unclear. We aimed to investigate the occurrence rate, predictors, and clinical outcomes of SIRS in patients with ALVOS after EVT.

Methods We retrospectively collected EVT data of patients with ALVOS from July 2014 to August 2019 in our center. SIRS in the absence of infection was defined as the presence of ≥ 2 of the following: (1) heart rate >90 (2) body temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, (3) white blood cells $>12\,000/\text{mm}^3$ or $<4000/\text{mm}^3$ or $>10\%$ bands for >24 h or (4) respiratory rate >20 . Favorable outcome was defined as obtaining a 90-day modified Rankin Scale (mRS) score ≤ 2 .

Results Among the 262 patients who received EVT, 92 (35.1%) developed SIRS, 88 (95.7%) of whom developed SIRS in the first two days after EVT. Patients who developed SIRS had a reduced favorable outcome (OR, 4.112 [95% CI, 1.705–9.920]; $P=0.002$) and higher mortality (OR, 25.236 [95% CI, 8.578–74.835]; $P<0.001$) at 90 days. Greater SIRS burden was positively correlated with NIHSS scores at discharge and mRS scores at 90 days ($r=0.249$, $P=0.017$; $r=0.230$, $P=0.027$). The development of SIRS in patients with ALVOS who underwent EVT was associated with neutrophilic leukocytosis, hyperglycemia, higher admission NIHSS scores, and worse collateral circulation.

Conclusions Patients with SIRS had higher odds of poor functional outcomes and higher mortality at 90 days in the EVT-treatment setting. The severity of the inflammatory response was positively correlated with the clinical outcomes of patients. Clinically relevant associations with SIRS were neutrophilic leukocytosis, hyperglycemia and baseline stroke severity, but favorable collateral circulation was a protective factor against SIRS.

Background

The inflammatory response is an important pathophysiological process of stroke [1]. Previous studies have shown that inflammation plays a dual role in particular stages of the stroke process, having both detrimental and beneficial effects [2–4]. On the one hand, the strong inflammatory reaction, characterized by the activation of resident glial cells, upregulation of pro-inflammatory cytokines, infiltration of leukocytes and monocytes, and breakdown of blood-brain barrier (BBB), may potentiate the secondary brain injury in the acute phase [3]. On the other hand, inflammation can contribute to propagating brain regeneration and recovery in the late postischemic phase [4]. Therefore, regulating inflammatory process of stroke may be a potential target for neuroprotective treatment [5].

Systemic inflammatory response syndrome (SIRS) is a continuous uncontrolled generalized inflammatory state. Clinical studies have shown that patients with more severe strokes have a higher risk of suffering from SIRS [6, 7], and the inflammatory response can be significantly attenuated by

successful thrombolysis [7]. Additionally, experimental studies have suggested that middle cerebral artery (MCA) occlusion stroke generates a cytokine-driven acute-phase inflammation [8, 9], which may lead to secondary brain damage and systemic inflammatory response, and the results vary depending on the presence of permanent or transient patterns [9].

Recently, endovascular treatment (EVT) has been validated to be safe and effective in patients with stroke caused by large vessel occlusions (LVO) in the anterior circulation [10]. However, even if timely and technically successful therapy is administered, nearly half of patients are unable to obtain functional independence [11]. Since leukocytes [12] and body temperature [13], two important components of SIRS, have been confirmed to contribute to poor functional outcomes in EVT-treated patients, we hypothesize that SIRS may affect the clinical outcomes of patients with acute large vessel occlusion stroke (ALVOS) after EVT.

Therefore, in the present study, we aimed to investigate the incidence of SIRS and the related influencing factors of the development of SIRS, and to determine whether the occurrence of SIRS is associated with functional outcomes in EVT-treated patients.

Methods

Patients Selection

We retrospectively reviewed all consecutive patients with ALVOS who underwent EVT at a comprehensive stroke center (Yijishan Hospital of Wannan Medical College) between July 2015 and August 2019. The study protocol was approved by the local ethics committee. The inclusion criteria were as follows: (1) time from onset to groin puncture (OTP) \leq 8 h; (2) baseline National Institutes of Health Stroke Scale (NIHSS) score \geq 6; (3) pretreatment Alberta Stroke Program Early Computerized Tomography (ASPECT) score \geq 6 and pre-stroke modified Rankin Scale (mRS) score $<$ 2; (4) occlusion of the internal carotid artery (ICA) or the MCA confirmed by computed tomographic angiography/magnetic resonance angiography/digital subtraction angiography (DSA); and (5) patients undergoing EVT. The flow chart for inclusion in the study population is displayed in Fig. 1.

For all enrolled patients, we recorded demographic data, personal medical history (atrial fibrillation, mellitus, hypertension), and stroke cause according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification, baseline ASPECT score, baseline NIHSS score, and thrombolytic therapy before EVT. Perioperative variables, including occlusion site, collateral circulation, modified Thrombolysis in Cerebral Infarction (mTICI) grading were recorded in detail by operators. In addition, postoperative imaging was assessed by two interventionalists (Ke Yang and Qian Yang) who were blinded to the clinical information. Blood samples were collected within 24 h after EVT.

Variable Definition

Collateral circulation was graded from absent to good collaterals (0–2) by the following criteria: grade 0 (no filling or < 1/3 filling of the occluded territory), grade 1 (\geq 1/3 but < 2/3 filling of the occluded territory), and grade 2 (\geq 2/3 filling of the occluded territory) [14]. Vessel recanalization after EVT, was assessed by the modified TICl scale, with scores of 0 to 2a defined as unsuccessful and scores of 2b to 3 defined as successful reperfusion. Functional outcome was assessed by the mRS at 90 days. Favorable outcome was defined as obtaining an mRS score \leq 2, indicating functional independence.

SIRS in the absence of infection was defined as the presence of \geq 2 of the following: (1) heart rate > 90, (2) body temperature > 38 °C or < 36 °C, (3) white blood cells > 12 000/mm or < 4000/mm or > 10% bands for > 24 h and (4) respiratory rate > 20 [15]. Patients with systemic inflammatory response caused by validated infection were excluded and placed in the control group. For patients with concurrent infection and systemic inflammatory response, we consulted two infectious disease experts to determine whether to include the patients in the case group. In addition, a scoring system was created to indicate SIRS severity. Each of the diagnostic indicators was 1 point, and the score was accumulated successively to calculate the SIRS score. It is worth noting that, if a patient was suffering from tachycardia atrial fibrillation (AF), the heart rate was not scored.

Statistical Analysis

We categorized patients according to the presence of SIRS, or favorable and unfavorable outcomes. Normally distributed continuous variables are summarized as the mean \pm SD, and nonnormally distributed continuous variables are expressed as the median and interquartile range (IQR). Categorical variables are presented as percentages. Differences between groups were analyzed using χ^2 tests, t tests, and Fisher's exact tests when appropriate. We employed Spearman correlation analysis to investigate the association between the SIRS burden and clinical outcomes (NIHSS score at discharge, 90-day mRS score). Univariate regression analysis was performed to evaluate the relationship between SIRS and clinical characteristics. Multivariate models were created to assess the impact of variables contributing to SIRS including variables with a $P < 0.10$ in univariate analysis. Similar models were applied to assess the prognostic impact of different outcome definitions.

Propensity score-matched (PSM) analysis was used to compare patients with direct EVT and bridging therapy with a caliper of 0.15 at a 1:1 ratio. The matched variables in the PSM of this study included age, sex, hypertension, AF, diabetes mellitus, baseline NIHSS score, baseline ASPECT score, OTP, occlusion site, and collateral status. IBM SPSS Statistics for Windows (version 25.0; IBM Corp, Armonk, NY) software and R version 3.4.3 (R Development Core Team, Vienna, Austria) were used for all statistical analyses.

Results

Patient Baseline Characteristics

Of the included patients, the mean age was 68.2 ± 11.6 years, the median baseline ASPECT score was 8 (IQR 8–10), and the median baseline NIHSS score was 16 (IQR 13–19). Additionally, 33 (12.6%) patients received bridging therapy, and 191 (72.9%) patients obtained successful recanalization. There were 114 patients (43.5%) who reached 90-day functional independence, and the overall mortality at 90 days after EVT was 25.6% (67). The baseline characteristics and outcomes of all enrolled patients are shown in Table 1.

Table 1
Demographics, baseline and outcome characteristics stratified by SIRS

| | All patients (n = 262) | Non-SIRS (n = 170) | SIRS (n = 90) | P value | Odds ratio (95% CI) | P value |
|--|---------------------------|-----------------------|------------------|---------|------------------------|---------|
| Age, mean (SD), y | 68.2 (11.6) | 68.1 (11.7) | 68.4 (11.6) | 0.839 | | |
| Male, n (%) | 142 (54.2) | 89 (52.4) | 53 (57.6) | 0.415 | | |
| Hypertension | 183 (69.8) | 109 (64.1) | 74 (80.4) | 0.006 | | |
| Diabetes mellitus | 43 (16.4) | 23 (13.5) | 20 (21.7) | 0.087 | | |
| Clinical characteristics, median (IQR) | | | | | | |
| Baseline NIHSS score | 16 (13–19) | 14 (12–18) | 18 (15–20) | < 0.001 | 1.115 (1.022–1.217) | 0.014 |
| Baseline ASPECT score | 8 (8–10) | 9 (8–10) | 8 (8–9) | 0.004 | | |
| Stroke cause, n (%) | | | | | | |
| LAA | 86 (32.8) | 61 (35.9) | 25 (27.2) | 0.183 | | |
| Cardioembolic | 145 (55.3) | 87 (51.2) | 58 (63.0) | | | |
| Undetermined or other | 31 (11.8) | 22 (12.9) | 9 (9.8) | | | |
| Occlusion site, n (%) | | | | | | |
| ICA | 112 (42.7) | 66 (38.8) | 46 (50.0) | 0.081 | | |
| MCA | 150 (57.3) | 104 (61.2) | 46 (50.0) | | | |
| OTP, mean (SD), min | 260 (210–300) | 260 (210–300) | 255 (210–300) | 0.565 | | |

SIRS, Systemic inflammatory response syndrome; ASPECT, Alberta Stroke Program Early CT; ICA, internal carotid artery; LAA, large-artery atherosclerosis; mTICI, modified thrombolysis in cerebral infarction; ICA, internal carotid artery; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; OTP, symptom onset to groin puncture time; FBG, fasting blood glucose

*Missing data in seven patients.

†Missing data in six patients

| | All patients (n = 262) | Non-SIRS (n = 170) | SIRS (n = 90) | <i>P</i> value | Odds ratio (95% CI) | <i>P</i> value |
|---|---------------------------|-----------------------|------------------|----------------|------------------------|----------------|
| Bridging therapy, n (%) | 33 (12.6) | 24 (14.1) | 9 (9.8) | 0.313 | | |
| Collateral score, n (%) | | | | | | |
| Grade 0 | 61 (23.3) | 24 (14.1) | 37 (40.2) | < 0.001 | Reference | |
| Grade 1 | 100 (38.2) | 64 (37.6) | 36 (39.1) | | 0.346 (0.153–0.783) | 0.011 |
| Grade 2 | 101 (38.5) | 82 (48.2) | 19 (20.7) | | 0.225 (0.093–0.545) | 0.001 |
| mTICI, 2b/3, n (%) | 191 (72.9) | 129 (75.9) | 62 (67.4) | 0.140 | | |
| Independence at 90 days, n (%) | 114 (43.5) | 101 (59.4) | 13 (14.1) | < 0.001 | | |
| Mortality at 90 days, n (%) | 67 (25.6) | 12 (7.1) | 55 (59.8) | < 0.001 | | |
| Laboratory examination | | | | | | |
| FBG*(mmol/L), mean (SD) | 7.4 (3.5) | 6.5 (2.6) | 8.9 (4.3) | < 0.001 | 1.140 (1.036–1.256) | 0.007 |
| Leucocytes [†] , 10 ⁹ /L | 10.2 (8.3–13.3) | 9.4 (7.9–11.3) | 13.7 (10.8–17.2) | < 0.001 | | |
| Neutrophils [†] , 10 ⁹ /L | 8.7 (6.8–11.6) | 7.7 (6.5–9.5) | 12.0 (10.8–17.2) | < 0.001 | 1.367 (1.219–1.534) | < 0.001 |
| Lymphocytes [†] , 10 ⁹ /L | 0.9 (0.7–1.3) | 1.0 (0.7–1.4) | 0.8 (0.6–1.2) | 0.011 | | |
| SIRS, Systemic inflammatory response syndrome; ASPECT, Alberta Stroke Program Early CT; ICA, internal carotid artery; LAA, large-artery atherosclerosis; mTICI, modified thrombolysis in cerebral infarction; ICA, internal carotid artery; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; OTP, symptom onset to groin puncture time; FBG, fasting blood glucose | | | | | | |
| *Missing data in seven patients. | | | | | | |
| †Missing data in six patients | | | | | | |

[insert Table 1 here]

Baseline Characteristics of All Patients Who Received EVT with SIRS Versus Non-SIRS

Of all the enrolled, 92 (35.1%) patients developed SIRS, of whom 57 (62.0%) developed SIRS on day 1, 31 (33.7%) on day 2, 1 (1.1%) on day 3, and 3 (3.3%) on day 4.

In the univariate analysis, the proportion of hypertension in patients with SIRS was higher than that in patients without SIRS (80.4% versus 64.1%; $P=0.006$). Patients with SIRS had higher baseline NIHSS scores (median, 18 versus 14; $P<0.001$) and lower pretreatment ASPECT scores (median, 8 versus 9; $P=0.004$). Poor collateral scores (grade 0, 40.2% versus 14.1%; grade 1, 39.1% versus 37.6%; grade 2, 20.7% versus 48.2%; $P<0.001$) were more common in patients with SIRS than in patients without SIRS (Table 1).

In addition, higher neutrophil counts (IQR 10.8–17.2) but lower lymphocyte counts (IQR 0.6–1.2) were found in patients who developed SIRS. Furthermore, patients with SIRS had significantly higher levels of fasting blood glucose (FBG: 8.92 ± 4.34 mmol/L versus 6.54 ± 2.56 mmol/L; $P<0.001$) than non-SIRS patients.

As expected, there were significant differences in both the entire range of mRS estimates and 90-day mortality between SIRS patients and non-SIRS patients. Compared with non-SIRS patients, in patients diagnosed with SIRS, favorable outcomes were less common (59.4% versus 14.1%; $P<0.001$). Nevertheless, 90-day mortality was proportionally higher in patients with SIRS than in patients without SIRS (59.8% versus 7.1%; $P<0.001$). However, we did not find a difference in the rate of successful reperfusion between the two groups (67.4% versus 75.9%; $P=0.140$).

In multivariate logistic analysis, increased neutrophils (odds ratio OR, 1.367 [95% CI: 1.219–1.534]; $P<0.001$), elevated FBG (OR, 1.140 [95% CI, 1.036–1.256]; $P=0.007$), and baseline NIHSS (OR, 1.115 [95% CI, 1.022–1.217]; $P=0.014$) were associated with SIRS development after endovascular treatment. However, good collaterals were associated with a reduced likelihood of suffering from SIRS (grade 1 versus grade 0: OR, 0.346 [95% CI 0.153–0.783]; $P=0.011$; grade 2 versus grade 0: OR, 0.225 [95% CI 0.093–0.545]; $P=0.001$; Fig. 2).

Systemic Inflammatory Response Syndrome and Outcomes

After adjusting for confounding factors including age, sex, stroke etiology, baseline NIHSS score and lymphocytes, the multivariate logistic analysis showed that the presence of SIRS (OR, 4.112 [95% CI, 1.705–9.920]; $P=0.002$; Table 2) was inversely associated with favorable functional outcomes at 90 days. The overall distribution of mRS scores at 90 days is shown in Fig. 3. Furthermore, there was a significant correlation between the presence of SIRS (OR, 25.236 [95% CI, 8.578–74.835]; $P<0.001$; Additional file 1: Table S1) and 90-day mortality. In addition, Spearman correlation analysis was adopted to explore the correlation between the severity of SIRS and clinical prognosis, and the results suggested

that SIRS severity was positively correlated with NIHSS scores at discharge and mRS scores at 90-days ($r = 0.237$, $r = 0.249$, $P < 0.05$).

Table 2

Comparison of variables between patients with and without a favorable outcome in the overall cohort

| | Favorable outcome (n = 114) | Poor outcome (n = 148) | P value | Odds ratio (95% CI) | P value |
|---|--|-----------------------------------|----------------|--------------------------------|----------------|
| Age, mean (SD), y | 65.7 (11.1) | 70.2 (11.7) | 0.002 | | |
| Male, n (%) | 70 (61.4) | 72 (48.6) | 0.040 | 2.043 (0.984–4.242) | 0.055 |
| Medical history, n (%) | | | | | |
| Hypertension | 75 (65.8) | 108 (73.0) | 0.209 | | |
| Diabetes mellitus | 12 (10.5) | 31 (20.9) | 0.024 | | |
| Clinical characteristics, median (IQR) | | | | | |
| Baseline NIHSS score | 14 (12–18) | 17 (14–20) | < 0.001 | | |
| Baseline ASPECT score | 9 (8–10) | 8 (8–9) | < 0.001 | 0.680 (0.491–0.942) | 0.020 |
| Stroke cause, n (%) | | | | | |
| LAA | 51 (44.7) | 35 (23.6) | < 0.001 | | |
| Cardioembolic | 47 (41.2) | 98 (66.2) | | | |
| Undetermined or other | 16 (14.0) | 15 (10.1) | | | |
| Occlusion site, n (%) | | | | | |
| ICA | 34 (29.8) | 78 (52.7) | < 0.001 | 2.663 (1.287–5.514) | 0.008 |
| MCA | 80 (70.2) | 70 (47.3) | | Reference | |
| OTP, mean (SD), min | 270 (225–302) | 250 (210–300) | 0.153 | | |
| Bridging therapy, n (%) | 16 (14.0) | 17 (11.5) | 0.538 | | |
| Collateral score, n (%) | | | | | |
| SIRS, Systemic inflammatory response syndrome; ASPECT, Alberta Stroke Program Early CT; ICA, internal carotid artery; LAA, large-artery atherosclerosis; mTICI, modified thrombolysis in cerebral infarction; ICA, internal carotid artery; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; OTP, symptom onset to groin puncture time; FBG, fasting blood glucose | | | | | |
| *Missing data in seven patients. | | | | | |
| †Missing data in six patients | | | | | |

| | Favorable outcome (n = 114) | Poor outcome (n = 148) | <i>P</i> value | Odds ratio (95% CI) | <i>P</i> value |
|---|--------------------------------|---------------------------|----------------|------------------------|----------------|
| Grade 0 | 8 (7.0) | 53 (35.8) | < 0.001 | Reference | |
| Grade 1 | 38 (33.3) | 62 (41.9) | | 0.344 (0.119–0.994) | 0.049 |
| Grade 2 | 68 (59.6) | 33 (22.3) | | 0.115 (0.038–0.343) | < 0.001 |
| mTICI, 2b/3, n (%) | 99 (86.8) | 92 (62.2) | < 0.001 | 0.223 (0.095–0.525) | 0.001 |
| SIRS, n (%) | 13 (11.4) | 79 (53.4) | < 0.001 | 4.112 (1.705–9.920) | 0.002 |
| Laboratory examination | | | | | |
| FBG* (mmol/L), mean (SD) | 6.1 (2.2) | 8.4 (3.9) | < 0.001 | | |
| Leucocytes [†] , 10 ⁹ /L | 9.3 (7.9–11.3) | 11.8 (8.9–14.8) | < 0.001 | | |
| Neutrophils [†] , 10 ⁹ /L | 7.7 (6.4–9.5) | 10.1 (7.4–12.7) | < 0.001 | 1.171 (1.032–1.328) | 0.015 |
| Lymphocytes [†] , 10 ⁹ /L | 1.1 (0.7–1.4) | 0.8 (0.6–1.2) | 0.005 | | |
| SIRS, Systemic inflammatory response syndrome; ASPECT, Alberta Stroke Program Early CT; ICA, internal carotid artery; LAA, large-artery atherosclerosis; mTICI, modified thrombolysis in cerebral infarction; ICA, internal carotid artery; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; OTP, symptom onset to groin puncture time; FBG, fasting blood glucose | | | | | |
| *Missing data in seven patients. | | | | | |
| †Missing data in six patients | | | | | |

[insert Table 2 here]

Systemic Inflammatory Response Syndrome and Bridging Therapy

The baseline demographics and outcomes of direct EVT and bridging therapy in the unmatched subgroups of patients are shown in Additional file 2: Table S2. After propensity score-matched analysis, 30 patients (mean age 66.7 ± 13.8 years, median NIHSS score 15 [IQR 14–18]) in the direct EVT group and 30 patients in the bridging therapy group (mean age 68.3 ± 12.0 years, median NIHSS score 16 [IQR 12–19]) were further compared. The neutrophil and leukomonocyte counts between these two groups were very similar ($P > 0.05$). The rate of SRIS did not differ between the two groups (40.0% versus 30.0%,

$P = 0.417$). Furthermore, the rate of 90-day mortality (20% versus 20%, $P = 1.000$) did not differ between the groups, nor did functional independence (40.0% versus 46.7%, $P = 0.602$) at 90 days (Additional file 2: Table S2).

Discussion

Our study systematically described the SIRS characteristics and clinical impact in patients with ALVOS after EVT. As key findings, first, we observed that the prevalence of SIRS (35.1%) was high and mainly occurred on the first and second days after EVT. Second, factors such as neutrophil activation, elevated FBG, and severity at admission, potentially contributing to SIRS, and good collateral circulation were protective factors for avoiding the occurrence of SIRS. Third, developing SIRS was detected to be independent associated with poorer functional outcomes in the overall distribution of mRS scores and mortality. Additionally, bridging therapy seemed to have no additional function on alleviating SIRS.

Previous studies aiming to elucidate the prevalence of SIRS have shown that approximately 18–53% of ischemic stroke patients experience SIRS in hospital [6, 7, 16], Boehme et al. [7] found about 20% of stroke patients treated with rt-PA developed SIRS, and the presence of SIRS was positively related to initial stroke severity and poor short-term functional outcomes. However, the outcomes of SIRS in patients after EVT remains unclear. To the best of our knowledge, this is the first study to assess the SIRS characteristics and clinical impact in EVT-treated patients.

In our study, we observed a high prevalence of SIRS (35.1%) in this setting. Furthermore, SIRS (95.7%) mainly occurred on the first and second day after EVT. The occurrence rate of SIRS in our study was higher than that of Boehme's (18%) but lower than that of Alicia's (53%) studies. This can be explained by the fact that our baseline NIHSS scores were higher than those of Boehme's study (Non-SIRS group median:14 versus 7; SIRS group median:18 versus 9). In Alicia's study, 69.2% of patients were posterior circulation stroke, which was the heat-regulating centers located in. In terms of the time of occurrence, we found that most cases of SIRS (95.7%) occurred in the first two days after EVT, which was consistent with the results of a previous study found that 79.1% of SIRS cases presented within 72 h after stroke [16]. A recently published study from Stanford used a single-cell mass cytometry approach to observe the systemic immune response to stroke in longitudinal blood samples from 24 patients over the course of 1 year and suggested the first 2 days as the acute phase of inflammation [17]. We speculate that several etiologies may explain this phenomenon. First, the time pattern of SIRS was parallel to the time course of neutrophil infiltration and inflammatory cytokine eruption [18–20]. Second, proinflammatory cytokines can lead to a delayed secondary opening of the BBB from 24 to 72 h after the onset of ischemia [20]. BBB dysfunction allows more circulating immune cells to enter the damaged brain tissues. The time pattern of SIRS may be instructive for future interventions. We consider that treatment interventions targeting postischemic inflammation should be mindful of temporal considerations by minimizing the detrimental potential of inflammation in the acute phase while enhancing its beneficial contributions to tissue repair in the late stages of ischemic stroke.

In our research, the development of SIRS in patients with ALVOS who underwent EVT was associated with neutrophil activation, elevated FBG and higher NIHSS scores upon hospital admission. During cerebral ischemia and reperfusion, leukocytes can adhere to vascular endothelial cells and block microvessels, leading to microvascular occlusion and the phenomenon of “no reflow”. Infiltrating neutrophils massively accumulate in ischemic cerebral tissue, where they abundantly release enzymes involving myeloperoxidase and elastase, and reactive oxygen species (ROS), which are known to cause local and systemic inflammation [21, 22]. Moreover, patients with high blood glucose levels are more likely to develop SIRS, which is in accordance with a previous study by Yoshimoto that indicated that plasma glucose was highly related to SIRS [23]. A prior study indicated that hyperglycemia may trigger massive accumulation of neutrophils, lead to endothelial damage and BBB disruption, and exacerbate downstream microvascular thromboinflammation (DMT) which precipitates neurovascular damage [24]. Consistent with previous observations, we observed that patients with more severe stroke indicated by higher NIHSS scores on admission had higher odds of developing SIRS [6, 7]. Audebert et al. [6] showed that SIRS depends on initial stroke severity. This implies that SIRS reflects the extent of tissue damage caused by stroke.

The quality of collateral circulation may affect the risk of SIRS after EVT. In the adjusted analysis, we observed that favorable collateral circulation protected patients from developing SIRS. In fact, collateral circulation provides access for leukocytes into the infarct core and penumbra [25]. However, interestingly, SIRS was significantly alleviated in the group with good collateral circulation. A generally accepted view is that the amount of collateral-dependent blood flow is one of the dominating determinants of infarct volume after LVO [26]. Therefore, rarefaction of the preexisting collateral circulation, results in more severe tissue injury and augmented neuronal necrosis following arterial occlusion; then, endogenous molecules are released from damaged cells amplifying inflammatory mediator expression and tissue damage by triggering and inducing the activation of Toll-like receptors (TLRs) [27], and some other damage-associated molecular patterns (DAMPs) [28]. Furthermore, collateral remodeling involves endothelial cell activation, leukocyte recruitment, matrix changes and cell proliferation; for patients with poor collateral circulation, the proinflammatory process involving angiogenesis will be more obvious [29].

Previous studies have shown that SIRS following ischemic stroke is associated with poorer short-term neurological outcomes and prolonged length of stay [7], but its long-term consequences, have been incompletely defined. Our study confirmed that the presence of SIRS was inversely associated with favorable functional outcomes at 90 days. Additionally, multivariate analysis showed that SIRS predicted increased 90-day mortality. Furthermore, the SIRS burden was positively correlated with NIHSS scores at discharge and mRS scores at 90 days. Our findings might encourage future research investigating whether regulating the inflammatory process during the acute phase can improve outcomes in EVT-treated patients. In fact, novel immunotherapeutic approaches have shown promising prospects in regulating inflammation and improving outcomes [30].

Notably, we did not find differences in the occurrence of SIRS between the patients with bridging therapy and the patients with direct EVT, which is in contract with a prior study. The study showed that stroke-

induced SIRS could be alleviated by successful thrombolysis [7]. We speculated that this may be related to the lower rate of intravenous thrombolysis in our center.

Several shortcomings should be noted. Our study was limited by its retrospective nature and monocentric design. Furthermore, many patients were transferred from the primary stroke center, and we did not review routine blood tests on admission due to economic reasons. Routine blood tests and other tests were not incomplete on admission. Finally, inflammatory markers such as highly sensitive C-reactive protein or various interleukin levels were not available.

Conclusions

In conclusion, SIRS is frequently present in patients with ALVOS who receive EVT and itself is an independent predictor of outcome. Future efforts towards understanding the pathogenesis governing the occurrence of SIRS may facilitate modulation of this inflammation by combining reperfusion therapies as a potential therapeutic strategy for acute large vessel occlusion stroke.

Abbreviations

SIRS
Systemic inflammatory response syndrome; ALOVS:Acute large vessel occlusion stroke;
EVT:Endovascular therapy; BBB:blood-brain barrier; MCA:middle cerebral artery; LVO:large vessel occlusions; OTP:onset to groin puncture; NIHSS:National Institute of Health Stroke Scale;
ASPECTS:Alberta Stroke Program Early Computerized Tomography ; mRS:modified Rankin Scale;
ICA:internal carotid artery; mTICI:modified Thrombolysis in Cerebral Infarction; IQR:interquartile range;
FBG, fasting blood glucose; ROS:reactive oxygen species; DMT:downstream microvascular thromboinflammation; TLRs:Toll-like receptors; DAMPs:damage-associated molecular patterns.

Declarations

Ethics Approval and Consent to Participate

The study was approved by The Research Ethics Committee of Wannan Medical College.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

XX, XH and ZZ planned and conceived the study. WW and LY collected the data. QY and QK analysed the image, JX, YZ, YX, and LG interpreted the data. XX, LY, WW, and XH wrote and critically revised the manuscript. All authors have read and approved the final manuscript.

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Figures

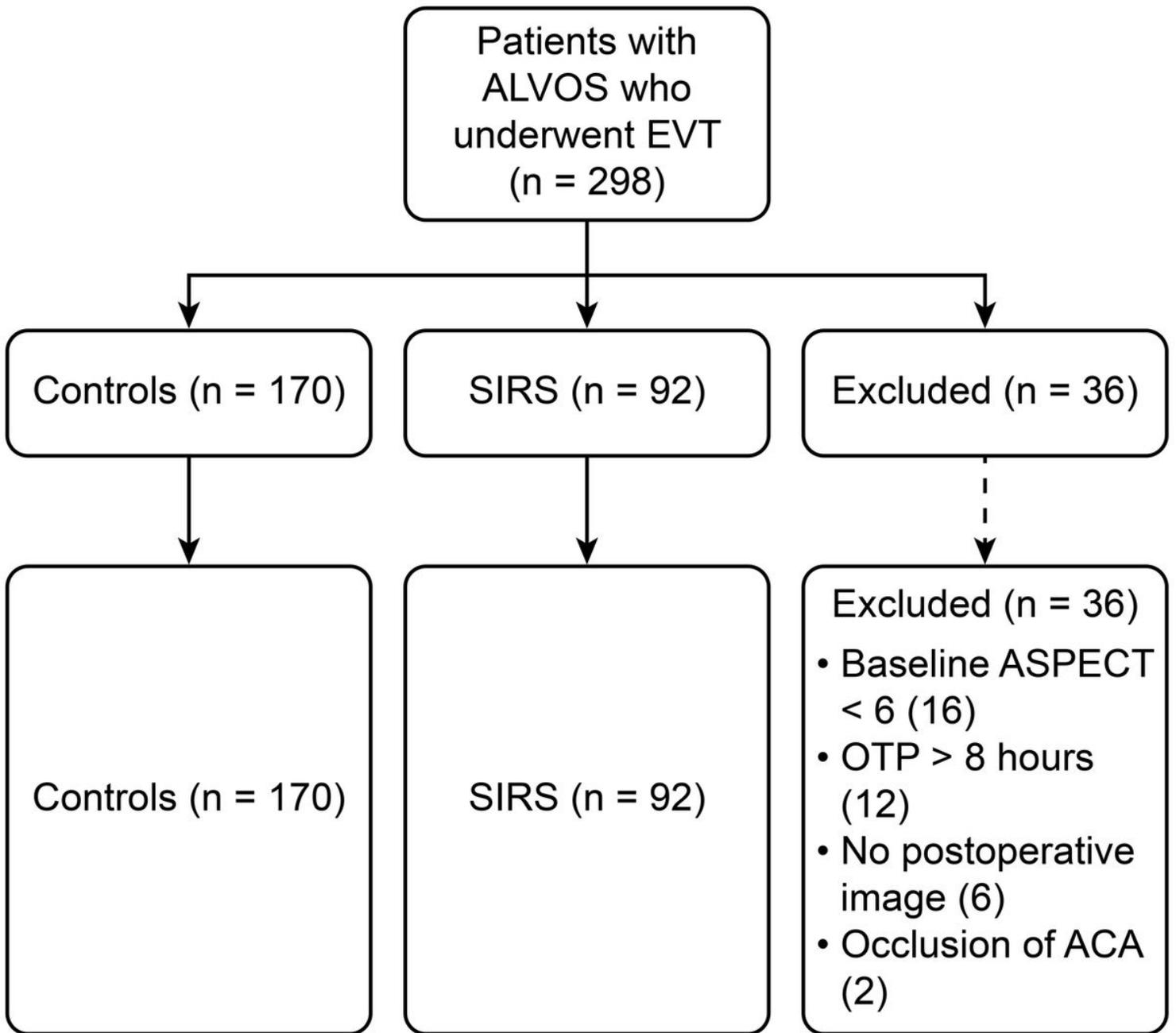


Figure 1

The flow chart for inclusion.

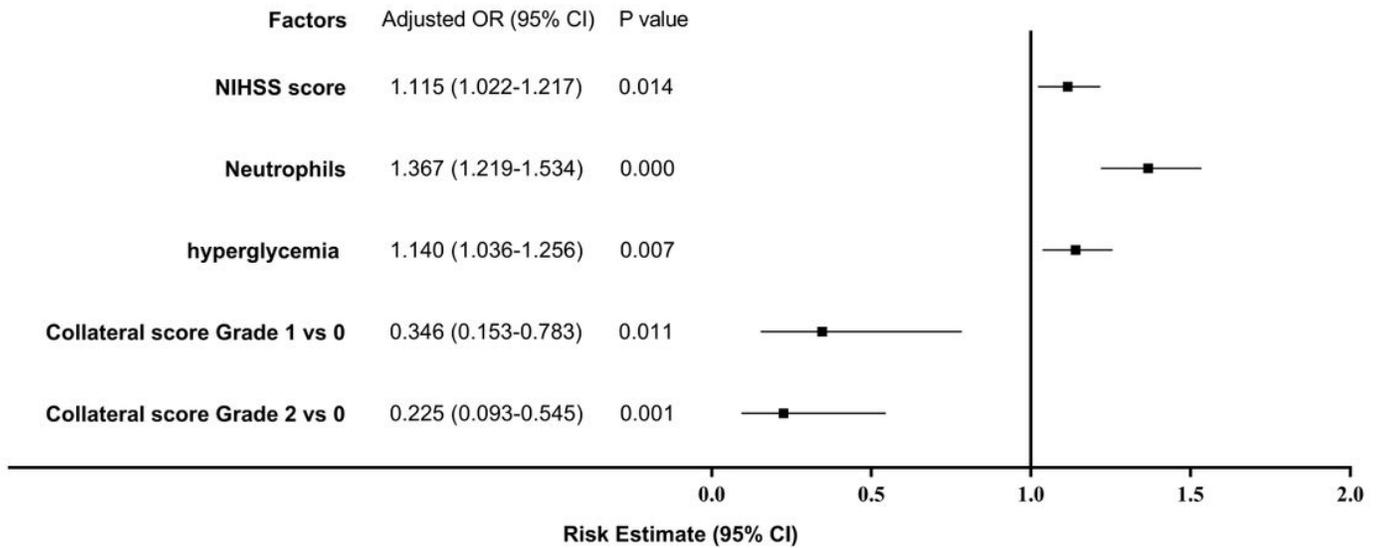


Figure 2

Odds ratios (OR) for the development of Systemic Inflammatory Response Syndrome (SIRS) in all patients.

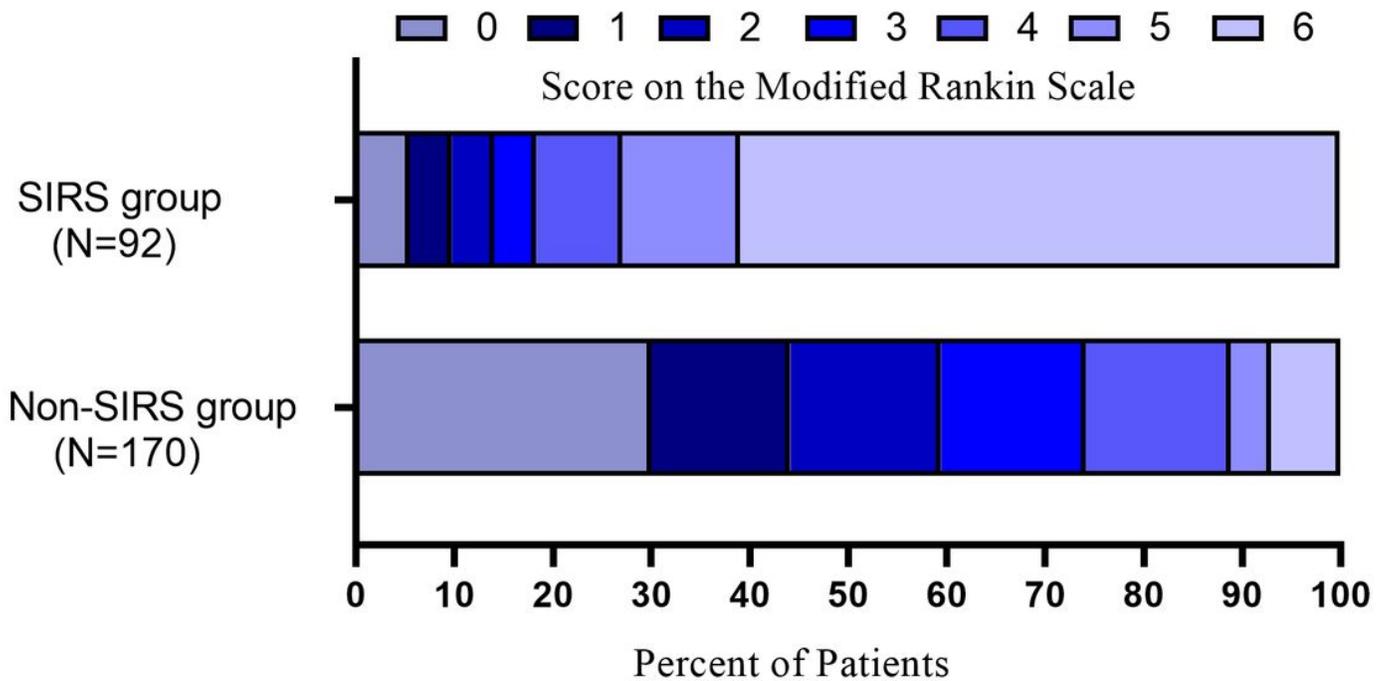


Figure 3

Distribution of mRS scores at 90 days according to the presence of SIRS.

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