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ORIGINAL RESEARCH

Association Between Inflammatory Burden Index and Unfavorable Prognosis After Endovascular Thrombectomy in Acute Ischemic Stroke

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Background: Inflammatory burden index (IBI) is a systemic inflammation indicator that reflects the inflammatory status. We aimed to investigate the prognostic value of IBI after endovascular thrombectomy (EVT) in patients with acute ischemic stroke.

Methods: We enrolled patients treated with EVT from a multicenter cohort between June 2020 and December 2021. The IBI was calculated as C-reaction protein × neutrophil / lymphocyte count. The primary outcome was the unfavorable functional outcome (90-day modified Rankin scale score 3–6). C-statistics and net reclassification indexes were used to assess the predictive accuracy. Multivariable logistic regression models were used to investigate the association between IBI and unfavorable outcome.

Results: A total of 295 patients (mean age, 64.0 ± 12.8 years; male, 63.7%) were enrolled in this study. In multivariable models, higher IBI levels were associated with an increased risk of 90-day unfavorable outcome after EVT (per 1-SD: odds ratio, 1.754; 95% confidence interval, 1.241–2.587; $P = 0.002$). Restricted cubic spline curve displayed a linear relationship between the IBI level and 90-day unfavorable outcome (P for nonlinearity = 0.410). Besides, IBI was a more accurate biomarker for predicting unfavorable outcomes with the highest predictive accuracy and reclassification indexes.

Conclusion: This study demonstrated that higher IBI was associated with an increased risk of 90-day unfavorable outcome in acute ischemic stroke treated with EVT.

Keywords: stroke, thrombectomy, inflammatory burden, systemic, prognosis

Introduction

Endovascular thrombectomy (EVT) has been recognized as an effective therapy for acute ischemic stroke (AIS) with large vessel occlusions in the anterior circulation.[1,2] Recently, the evidence from randomized controlled trials has confirmed the efficacy and safety of EVT in patients with large cores.[3] However, the efficacy of EVT is limited by early complications, such as symptomatic intracranial hemorrhage (sICH),[4] futile recanalization,[5] malignant brain edema,[6] and early neurology stability.[7] Previous studies reported that nearly 50% of the patients treated with EVT remained functional dependence at 90 days.[8] Hence, it is urgent to find simple and powerful biomarkers for predicting the prognosis of EVT to prompt the rapid identification of the high-risk patients and improve functional assessments.

Systemic inflammation plays an important role in causing tissue damage after the pathogenic stimuli in different tissues.[9] Previous studies had shown that systematic inflammation was associated with the progression of cerebral ischemic lesions through remodeling and infarct resolution in the brain tissue.[10,11] Recently, several studies found that lowing systematic inflammation in the acute phase was associated with the improved tissue salvage and reduced risk of vascular events.[12,13] Systemic inflammation can be manifested by changes in the peripheral inflammatory parameters,

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such as neutrophils, lymphocytes, platelets, and C-reactive protein (CRP). Inflammatory burden index (IBI) is calculated from neutrophils, lymphocytes, and CRP.[14] Previous studies had shown that IBI was an independent predictor for the prognosis of different malignancies and may be the optimal indicator among various systemic inflammation indicators.[14–16] However, few studies are available regarding the prognostic value of IBI for the clinical outcomes of AIS. Hence, we performed a retrospective analysis of a multicenter cohort and aimed to assess the relationship between IBI and unfavorable prognosis in AIS patients treated with EVT.

Methods

Data that support the findings of this study are available from the corresponding authors upon reasonable request.

Study Population

This study was a retrospective cohort study with prospective data collection. We enrolled patients diagnosed with AIS and treated with EVT from 3 comprehensive centers: Nanjing brain hospital, Nanjing first hospital, and Yijishan Hospital between June 2020 and December 2021. This study was performed in accordance with the 1964 Helsinki Declaration and was approved by the ethics committees of each participating center (2019-kyy121–01). All patients or their legally authorized representatives provided the written informed consents.

Patients were included according to the following criteria: (1) aged ≥18 years; (2) diagnosis of AIS due to large vessel occlusion in the anterior circulation; (3) treated with EVT within 6 hours of stroke onset or met the DAWN or DEFUSE criteria within the extended time window;[17,18] (4) pre-stroke modified Rankin Scale score (mRS) score <2. We excluded patients if they: (1) had missing routine blood examinations and follow up information; (2) had active infections within three days before treatment; (3) had chronic inflammatory diseases or taking corticosteroids; (4) had autoimmune diseases or a history of tumors.

Data Collection

Demographic and clinical data, medial history, laboratory data, procedural parameters and vital signs were retrospectively collected. Stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS).[19] Computed tomography was routinely performed at admission and repeated within 24 hours after EVT or at any time of symptom deterioration. Radiological findings were independently reviewed by two experienced neurologists blinded to this study. Cerebral ischemia was assessed by the Alberta Stroke Program Early CT score (ASPECTS).[20] Collateral circulation was assessed by the American Society of Interventional and Therapeutic Neuroradiology / Society of Interventional Radiology collateral vessel grading system. Successful recanalization was defined as modified Thrombolysis in Cerebral Ischemia score of 2b or 3. Symptomatic intracranial hemorrhage (sICH) was defined according to the European Cooperative Acute Stroke Study (ECASS-III) criteria.[21]

Endovascular Treatment

Intravenous thrombolysis was initiated within 4.5 hours after the onset of symptoms. Therapeutic decisions of bridging therapy or direct EVT were based on the judgement of physicians. EVT was performed by experienced interventionists using stent retrievers, aspiration thrombectomy, or the combination of both techniques.

Systemic Inflammatory Indicators

We routinely collected laboratory results, including routine blood, blood chemistry, and other serological test from peripheral venous blood samples before EVT and intravenous thrombolysis treatment. The systemic inflammatory indicators were calculated with the following equations from laboratory results: IBI = CRP × (neutrophil count / lymphocyte count), neutrophil-to-lymphocyte ratio (NLR) = neutrophil count / lymphocyte count; platelet-to-lymphocyte ratio (PLR) = platelet count / lymphocyte count, systemic-immune-inflammation index (SII) = platelet count × (neutrophil count / lymphocyte count).

Follow Up and Clinical Outcome

In this study, the functional statuses of the enrolled patients were systematically assessed by trained neurologists via clinical interviews or phone calls at 90 days after the index stroke. The primary outcome was the unfavorable outcome of patients treated with EVT, which was defined as a mRS score of 3–6 at 90 days.

Statistical Analyses

Data were expressed as frequencies and percentages for categorical variables and mean ± standard deviation or median (interquartile range, [IQR]) for continuous variables. We test the normality using the Kolmogorov–Smirnov test. Differences between groups were compared with chi-square tests or Fisher's exact tests for categorical variables *t*-test or Mann–Whitney *U*-test for continuous variables as appropriate.

We used the receiver operative characteristic curve and Delong test to evaluate the predictive accuracy of systematic inflammatory indicators for unfavorable outcome after EVT. The optimal cut-off value of IBI was determined using the maximally selected rank statistic method.[22] Multivariable logistic regression models were used to investigate the association between IBI (per 1-SD increase and quartiles) and unfavorable outcome after EVT. Model 1 was an unadjusted model. Model 2 was adjusted for age, sex, and potential predictors for unfavorable outcome such as: hypertension, diabetes mellitus, atrial fibrillation, hyperlipidemia, coronary heart disease, heart failure, smoking, drinking, NIHSS score, ASPECTS score and intravenous thrombolysis treatment. Model 3 was adjusted for variables with P <0.10 in univariate analyses and other inflammatory biomarkers using the back-ward elimination method.

We used the restricted cubic spline curve with 4 knots (5th, 35th, 65th, and 95th percentiles) to assess the nonlinear relationship between IBI and unfavorable outcome adjusted for covariates finally included in the model 3,[23] and the relationship was linear when the P value was greater than 0.05. Subgroup analysis was used to assess the robustness of the association between IBI and unfavorable outcome according to age, sex, NIHSS score, and intravenous thrombolysis. Furthermore, we used the net improvement index (NRI) to evaluate the improvement of the predictive accuracy after adding each systematic inflammatory indicator into model 3, respectively,[24] which can compare the predictive accuracy between the original model and the original model added with systematic inflammatory indicators.

Statistical analyses were performed using R version 4.2.2. (R Foundation, Vienna, Austria), and a two-sided P value <0.05 was considered to be statistically significant.

Results

A total of 295 patients were enrolled in this study after excluding 18 patients with missing routine blood examinations and follow up information, 11 patients with active infections within three days, 4 patients with chronic inflammatory diseases and 3 patients with autoimmune diseases or hematological tumors. The baseline characteristics of patients were shown in Table 1. The mean age was 64.0 ± 12.8 years and 188 (63.7%) patients were male. The median value of IBI was 40.2 [12.6, 141.2] mg/L. 101 (34.2%) patients received intravenous thrombolysis treatment and 250 (84.7%) had successful recanalization. 23 (7.8%) patients developed sICH and 131 (44.4%) patients had 90-day unfavorable outcome after EVT. Compared to patients with favorable outcome, those with 90-day unfavorable outcome were older, had a higher proportion of hypertension, diabetes mellitus, atrial fibrillation, heart failure, internal carotid artery occlusion and successful recanalization, had lower ASPECTS scores, had higher systolic blood pressures, NIHSS scores, neutrophil counts, CRP, fasting blood glucose, IBI, NLR, and SII (all P <0.05).

Among the systematic inflammatory indicators, the IBI had the highest C-statistic (0.658; 95% CI, 0.598–0.659; Figure 1) for predicting 90-day unfavorable outcome after EVT. The results of the Delong test between IBI and other inflammatory biomarkers were 0.112 for NLR, 0.038 for SII, 0.002 for PLR. The optimal cut-off value of IBI was 23.59 mg/L in the maximally selected rank statistic method. Univariable analyses revealed that age, hypertension, diabetes mellitus, atrial fibrillation, heart failure, systolic blood pressure, NIHSS score, ASPECTS score, Neutrophil count, CRP, fasting blood glucose, occlusion site, collateral circulation, successful recanalization, type of procedure, and sICH were significant predictors for 90-day unfavorable outcome after EVT (all P <0.05; Supplementary Table 1).

Table 1 Baseline Characteristics of Patients Overall and by Functional Outcomes After EVT

Variable	Overall (n = 295)	Unfavorable Outcome (n = 131)	Favorable Outcome (n = 164)	*P* value
Age (years)	64.0 (12.8)	68.0 (11.4)	60.8 (13.1)	<0.001
Male, n (%)	188 (63.7)	86 (65.6)	102 (62.2)	0.623
Medical history, n (%)				
Hypertension	192 (65.1)	95 (72.5)	97 (59.1)	0.023
Diabetes mellitus	56 (19.0)	34 (26.0)	22 (13.4)	0.010
Atrial fibrillation	118 (40.0)	62 (47.3)	56 (34.1)	0.030
Hyperlipidemia	24 (8.1)	9 (6.9)	15 (9.1)	0.620
Coronary heart disease	67 (22.7)	34 (26.0)	33 (20.1)	0.295
Heart failure	27 (9.2)	18 (13.7)	9 (5.5)	0.025
Smoking	86 (29.2)	33 (25.2)	53 (32.3)	0.227
Drinking	59 (20.0)	25 (19.1)	34 (20.7)	0.838
Clinical assessment				
Systolic BP (mmHg)	146.7 (24.9)	150.2 (25.7)	143.8 (24.0)	0.029
Diastolic BP (mmHg)	85.0 (14.6)	86.5 (15.0)	83.7 (14.2)	0.100
NIHSS score	16.0 [12.0, 20.0]	18.0 [14.0, 22.0]	13.5 [10.0, 18.0]	<0.001
ASPECTS score	9.0 [8.0, 10.0]	9.0 [7.0, 10.0]	10.0 [8.0, 10.0]	0.001
Laboratory data				
White blood cell count ($\times 10^9$/L)	9.9 (4.0)	10.4 (4.5)	9.5 (3.6)	0.060
Neutrophil count ($\times 10^9$/L)	8.0 (3.8)	9.0 (4.3)	7.2 (3.1)	<0.001
Lymphocyte count ($\times 10^9$/L)	1.3 (0.7)	1.3 (0.8)	1.3 (0.7)	0.427
Platelet count ($\times 10^{12}$/L)	174.0 [144.0, 212.0]	174.0 [143.5, 214.0]	172.5 [146.2, 210.2]	0.737
C-reactive protein (mg/L)	7.3 [2.0, 17.8]	11.1 [3.7, 31.2]	5.5 [1.4, 12.7]	<0.001
Fasting blood glucose (mmol/L)	6.8 [5.7, 8.4]	7.3 [6.0, 9.1]	6.5 [5.5, 7.8]	<0.001
Intravenous thrombolysis, n (%)	101 (34.2)	43 (32.8)	58 (35.4)	0.739
Door to puncture (min)	136.3 (84.4)	139.5 (83.8)	133.8 (85.1)	0.564
Puncture to reperfusion (min)	94.8 (57.5)	95.3 (54.1)	94.3 (60.3)	0.880
Occlusion site, n (%)				0.009
ICA	120 (40.7)	66 (50.4)	54 (32.9)	
MCA/ACA (M1/A1)	171 (58.0)	64 (48.9)	107 (65.2)	
MCA/ACA (M2/A2)	4 (1.4)	1 (0.8)	3 (1.8)	
ASITN/SIR 2–3, n (%)	134 (45.4)	51 (38.9)	83 (50.6)	0.060
Type of procedure, n (%)				0.068
Stent retriever first	145 (49.2)	66 (50.4)	79 (48.2)	
Aspiration first	124 (42.0)	59 (45.0)	65 (39.6)	
Angioplasty or stent first	26 (8.8)	6 (4.6)	20 (12.2)	
mTICI 2b/3, n (%)	250 (84.7)	100 (76.3)	150 (91.5)	0.001
sICH, n (%)	23 (7.8)	18 (13.7)	5 (3.0)	0.001
Systemic inflammatory indicators				
IBI (mg/L)	40.2 [12.6, 141.2]	80.6 [24.5, 336.6]	26.2 [8.1, 99.1]	<0.001
NLR (%)	6.1 [3.9, 11.8]	7.4 [4.4, 14.2]	5.7 [3.7, 8.5]	0.001
SII ($\times 10^{12}$/L)	1130.7 [650.0, 1969.9]	1344.6 [734.1, 2222.0]	942.3 [625.8, 1604.7]	0.006
PLR (%)	148.3 [107.1, 216.4]	160.7 [109.2, 229.1]	144.9 [106.2, 204.2]	0.238

Abbreviations: ACA, anterior cerebral artery; ASITN/SIR, the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology; ASPECTS, the Alberta Stroke Program Early Computed Tomography Score; BP, blood pressure; EVT, endovascular treatment; IBI, inflammatory burden index; ICA, internal carotid artery; MCA, middle cerebral artery; mTICI, modified Thrombolysis in Cerebral Infarction Score; NIHSS, National Institute of Health Stroke Scale; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; sICH, symptomatic intracranial hemorrhage; SII, systemic-immune-inflammation index.

In multivariable analyses, IBI was significantly associated with unfavorable outcome in model 1 (per 1-SD: odds ratio [OR], 1.805; 95% CI, 1.336–2.578; P <0.001; quartile 3 versus quartiles 1: OR, 3.218; 95% CI, 1.799–5.861; P <0.001), model 2 (per 1-SD: OR, 1.945; 95% CI, 1.372–2.861; P <0.001; quartile 3 versus quartiles 1: OR, 2.908; 95% CI, 1.485–

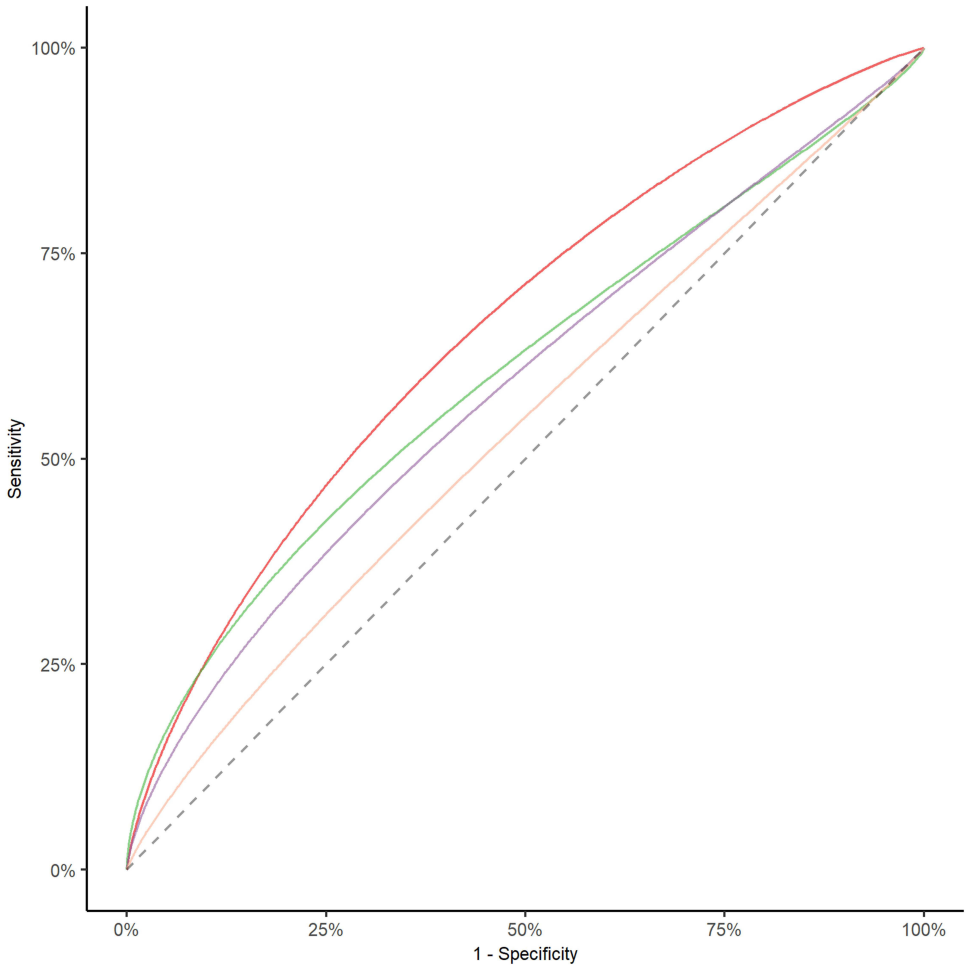

Figure 1 Receiver operating characteristic curves of systemic inflammatory indicators for unfavorable outcome after EVT. The AUC was 0.658 (0.598–0.659) in red line for IBI, 0.605 (0.545–0.606) in green line for NLR, 0.586 (0.523–0.587) in purple line for SII, 0.537 (0.468–0.537) in Orange line for PLR.
Abbreviations: AUC, area under the curve; EVT, endovascular treatment; IBI, inflammatory burden index; NLR, neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; SII, systemic-immune-inflammation index.

5.810; $P = 0.002$), and model 3 adjusted for the selected variables after the backward elimination method: age, fasting blood glucose, heart failure, NIHSS score, ASPECTS score, mTICI, and sICH (per 1-SD: OR, 1.754; 95% CI, 1.241–2.587; $P = 0.002$; quartile 3 versus quartiles 1: OR, 2.564; 95% CI, 1.296–5.158; $P = 0.007$; Table 2 and Supplementary Table 2).

Table 2 Multivariable Analyses for the Association Between IBI and Unfavorable Outcomes After EVT

IBI, mg/L	Model 1		Model 2		Model 3	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Per 1-SD increase	1.805 (1.336–2.578)	<0.001	1.945 (1.372–2.861)	<0.001	1.754 (1.241–2.587)	0.002
Quartiles						
≤18.82	Ref		Ref		Ref	
18.82–97.38	2.135 (1.193–3.87)	0.011	1.601 (0.819–3.152)	0.169	1.400 (0.708–2.777)	0.333
>97.38	3.218 (1.799–5.861)	<0.001	2.908 (1.485–5.810)	0.002	2.564 (1.296–5.158)	0.007

Notes: Model 1: unadjusted model. Model 2: adjusted for age, sex, hypertension, diabetes mellitus, atrial fibrillation, hyperlipidemia, coronary heart disease, heart failure, smoking, drinking, NIHSS score, ASPECTS score and intravenous thrombolysis treatment. Model 3: adjusted for the selected variables after the backward elimination method: age, fasting blood glucose, heart failure, NIHSS score, ASPECTS score, mTICI, and sICH.
Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CI, confidence interval; EVT, endovascular treatment; IBI, inflammatory burden index; mTICI, modified Thrombolysis in Cerebral Infarction Score; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; sICH, symptomatic intracranial hemorrhage.

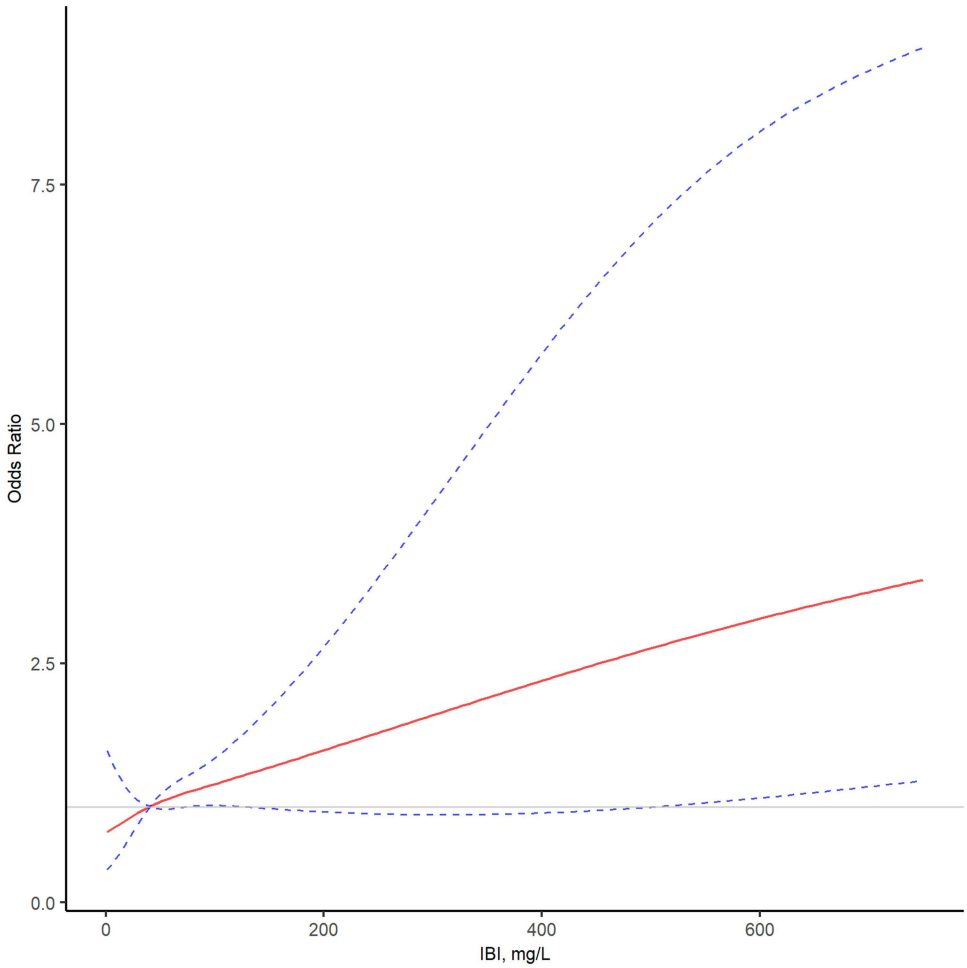

Figure 2 The association between IBI and unfavorable outcome after EVT. *P* for nonlinearity = 0.410. The restricted cubic spline was adjusted for covariates in model 3 with the median value of IBI (40.24 mg/L) as reference.
Abbreviations: IBI, inflammatory burden index; EVT, endovascular treatment.

The multivariable restricted cubic spline curve showed a linear and increasing relationship between IBI and the risk of 90-day unfavorable outcome after EVT (*P* for nonlinearity = 0.410; Figure 2). The reclassification index analysis revealed that IBI had the highest improvement of the predictive accuracy compared with other systematic inflammatory indicators (NRI, 0.332; 95% CI, 0.029–0.635; *P* = 0.036; Table 3). In addition, the association between IBI and 90-day unfavorable outcome was similar across different subgroups stratified by age, sex, NIHSS score and intravenous thrombolysis treatment (all *P* for interaction >0.05; Figure 3).

Table 3 Net Reclassification Index for Systemic Inflammatory Indicators

Indexes	NRI (95% CI)	*P* value
IBI	0.332 (0.029–0.635)	0.036
NLR	0.159 (−0.015–0.419)	0.187
SII	0.056 (−0.018–0.404)	0.630
PLR	0.017 (−0.022–0.122)	0.652

Abbreviations: CI, confidence interval; IBI, inflammatory burden index; NLR, neutrophil-to-lymphocyte ratio; NRI, net reclassification index; PLR, platelet-to-lymphocyte ratio; SII, systemic-immune-inflammation index.

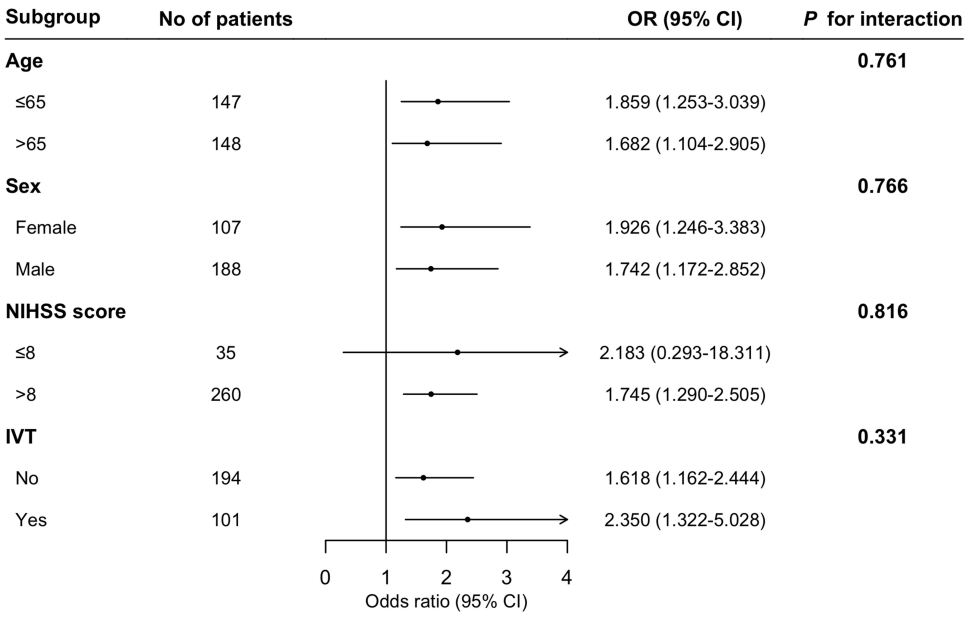

Figure 3 Subgroup analyses for the association between IBI and unfavorable outcome after EVT. The solid lines and points represented the odds ratio and the corresponding 95% confidence interval.
Abbreviations: CI, confidence interval; EVT, endovascular treatment; IBI, inflammatory burden index; OR, odds ratio.

Discussion

In this multicenter study of 295 patients with AIS treated with EVT, we investigated the association between systemic inflammation indicators and 90-day unfavorable outcome. We found that IBI was positively related to the risk of unfavorable outcome after adjusting for important prognostic covariates and might be considered a target for attenuation therapy for systemic inflammation. Compared with other inflammatory markers, IBI was a more accurate biomarker for predicting unfavorable outcomes with the highest area under the curve and reclassification indexes.

Previous studies had shown that systemic inflammation was closely associated with clinical prognosis of AIS patients. The proportion of patients with 90-day unfavorable outcome in our study (44.4%) was comparable to previous findings. Yao et al retrospectively evaluated the association between dynamic inflammatory markers and unfavorable outcome of AIS patients who achieved complete reperfusion after EVT. They found that the NLR measured at 24h and 3–7 day were independent predictors for 90-day unfavorable outcome, which could improve the diagnostic accuracy of the conventional characteristics.[25] Chen et al found that platelet volume markers were correlated with stroke severity and NLR levels were independent predictors of 90-day unfavorable outcome after EVT.[23] Pikija et al found that NLR was an independent predictor for intracranial hemorrhage after EVT and the post-stroke immune system may influence the pathophysiological development of intracranial hemorrhage.[24]

BI is a newly developed biomarker that comprehensively reflects the inflammatory status. Previous studies suggested that IBI may be a better choice for predicting the prognosis of patients with different malignancies. Song et al systemically assessed the prognostic ability of IBI for the primary hepatocellular carcinoma and compared IBI with traditional inflammatory indicators, such as NLR, PLR, and SII. They found that IBI was the optimal predictor compared with other indicators with area under the curve of 0.698.[16] Xie et al explored the association between IBI and the overall survival rate of 6359 patients with common cancers and demonstrated that the grading system based on stratified IBI levels could function as the reference for evaluating the clinical prognosis of cancers.[14] Xie et al also re-evaluated results in patients with non-small cell lung cancer and proposed that IBI was the optimal inflammatory biomarker among systemic inflammation-related biomarkers.

The advantage of IBI over other inflammatory indicators may lie in its measurement of the balance between immune and acute inflammation by combining hematological biomarkers of neutrophils, lymphocytes and CRP.[26] The possible mechanisms of IBI and unfavorable prognosis might be explained as follows. First, neutrophils can prompt the release of

free oxygen radicals and matrix metalloproteinase-9, which is an important predictor for hemorrhage transformation and secondary brain injury.[27–29] Second, cerebral ischemic tissues can release inflammatory cytokines and chemokines, which guides the concentration of the leukocytes and may have neuroprotective effect on the neurological function.[10,30] Third, CPR is a well-established inflammatory biomarker and is related to the ischemia-reperfusion injury, post-stroke infection, and inflammatory stimuli.[31,32]

To the best of our knowledge, this was the first study to investigate the association between IBI and unfavorable outcome after EVT. However, this study had several limitations. First, this was a multi-center study with a small sample size, which might generate biases due to the differences in the treatment preferences and experiences of each participating center. Second, systemic inflammatory indicators were only measured at a single time point before EVT and intravenous thrombolysis, and the dynamic changes of these indicators would be affected by intravenous thrombolysis. Third, several potentially prognostic indicators were not available due to the retrospective design of this study, such as calcitonin, interleukin-1 and calprotectin. Finally, larger prospective cohorts were warranted to further explore the role of IBI in guiding the treatment of lowing systemic inflammation in AIS patients treated with EVT.

In conclusion, our study showed that higher IBI was an independent predictor for unfavorable outcome after EVT. These results suggested that IBI can be helpful to assess the inflammatory burden of AIS patients, and may provide individual references for anti-inflammatory treatments such as recombinant human IL-1 receptor antagonist,[33] minocycline,[34] and fingolimod.[35]

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Disclosure

The authors report no conflicts of interest in this work.

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