Journal of Inflammation Research

Dovepress
Taylor & Francis Group

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ORIGINAL RESEARCH

Predictive Value of Epicardial Adipose Tissue for Hemorrhagic Transformation and Functional Outcomes in Acute Ischemic Stroke Patients Undergoing Intravenous Thrombolysis Therapy

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Purpose: Hemorrhagic transformation (HT) is a severe complication in patients with acute ischemic stroke (AIS) undergoing intravenous thrombolysis therapy (IVT). Epicardial adipose tissue (EAT) contributes to the development of AIS and the disruption of the blood-brain barrier. This study aims to investigate the relationship between EAT and the risk of HT, as well as functional outcomes, in AIS patients treated with IVT.

Patients and Methods: 230 AIS patients were included. Epicardial adipose tissue volume (EATV) and EAT attenuation were measured from chest CT scans. Follow-up cranial CT or magnetic resonance imaging (MRI) assessed HT occurrence. Patients were stratified into groups based on the presence of HT or parenchymal hematoma (PH), and their 90-day functional outcomes (evaluated by the modified Rankin Scale).

Results: HT occurred in 52 (22.61%) patients, including 28 (12.17%) patients with PH, 85 (37.00%) patients had poor 90-day functional prognosis. Compared to the first quartile of EATV, the third quartile (OR 9.254, 95% CI 1.533–55.853) and the fourth quartile (OR 11.117, 95% CI 1.925–64.211) of EATV were independent predictors of HT; and EATV as a continuous variable (OR 1.022, 95% CI 1.005–1.040) was an independent risk factor for PH. Higher EAT attenuation was independently associated with poor prognosis (OR 1.170, 95% CI 1.056–1.297). The area under curve for predicting HT, PH and 90-day poor functional outcome was 0.705 (95% CI 0.632–0.778), 0.693 (95% CI 0.597–0.789), and 0.720 (95% CI 0.653–0.787).

Conclusion: The study demonstrates that EAT is associated with HT and poor 90-day outcomes in AIS patients undergoing IVT.

Keywords: epicardial adipose tissue, inflammation, hemorrhagic transformation, ischemic stroke, intravenous thrombolysis, early neurological deterioration

Introduction

Ischemia and hypoxia can increase the permeability of the blood-brain barrier (BBB) and disrupt the vascular basement membrane early in AIS. Intravenous thrombolysis therapy (IVT) with recombinant tissue plasminogen activator (rt-PA) is considered the preferred treatment for acute ischemic stroke (AIS) within 4.5 hours of symptom onset,[1] significantly improving the clinical prognosis.[2]

Although rt-PA is effective in dissolving thrombi, it can also induce reperfusion injury by mediating neurovascular inflammation and activating blood coagulation pathway. This can exacerbate BBB disruption and increase the risk of intracranial hemorrhage transformation (HT).[3,4] HT is a severe complication of rt-PA treatment, associated with early neurological deterioration, higher disability rates, increased mortality, and poorer clinical outcomes.[5] Therefore, identifying the risk factors for HT after IVT is crucial for enhancing the management of AIS during the hyperacute phase.

Received: 16 October 2024
Accepted: 21 December 2024
Published: 31 December 2024

Epicardial adipose tissue (EAT), situated between myocardium and pericardial visceral layer, closely is in close proximity to the myocardium and coronary arteries.[6] EAT secretes bioactive substances, including pro-inflammatory and pro-atherosclerotic factors, which influence local tissues via paracrine and vascular mechanisms, thereby promoting coronary atherosclerosis.[7] Furthermore, these substances can enter systemic circulation, inducing a chronic inflammatory state that leads to vascular dysfunction in organs beyond the heart.[8,9] The EAT attenuation serves as a novel inflammatory marker associated with various diseases.[10] Evidence suggests that chronic systemic inflammatory response induced by EAT may be linked to the incidence of AIS,[11] with higher levels of visceral fat correlating with poorer outcome following thrombolysis in AIS patients.[12] Nonetheless, the specific relationship between EAT, HT and prognosis following rt-PA thrombolysis remains to be fully elucidated.

This study aims to investigate the relationship between EAT and HT, as well as 90-day functional outcomes after IVT in AIS patients. Specifically, it assesses whether higher EATV could serve as a predictive risk factor for HT following IVT.

Materials and Methods

Patients

This retrospective study recruited AIS patients who received IVT at the West Coast Campus of The Affiliated Hospital of Qingdao University between January 2022 and October 2023. All participants received rt-PA treatment within 4.5 hours of symptom onset. The rt-PA dosage was 0.9 mg/kg, administered intravenously over 1 hour, with a maximum dose of 90 mg. Of this, 10% was given as an intravenous bolus within the first minute. Following rt-PA administration, all patients underwent standardized sequential treatment.[13]

Inclusion criteria: (1) age > 18 years old; (2) adherence to the "Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2018",[13] and administration of rt-PA treatment within 4.5 hours of symptom onset; (3) availability of complete clinical data. Exclusion criteria: (1) incomplete clinical data; (2) absence of new infarct lesions on subsequent imaging examinations; (3) presence of cerebral vascular malformations; (4) underwent further related surgical treatments following IVT; (5) history of cardiac or thoracic surgery; (6) lack of 90-day follow-up data; (7) presence of infections, inflammations, blood disorders, or immune disorders before IVT; (8) other determined etiologic subtypes and undetermined etiologic subtypes of AIS according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST). It is important to note that because the patients we included did not include those undergoing immunosuppressive/modulant drugs and those with cancer, this was not indicated in our exclusion criteria. This retrospective review study was in accordance with the ethical standards of the 1975 Declaration of Helsinki. And the Ethics Committee of Affiliated Hospital of Qingdao University approved this study (ethical number: QYFY WZLL 29375). Given the retrospective nature of the study, the requirement for consent was waived in accordance with the approval of the Ethics Committee.

Date Collection

(1) Peripheral venous blood samples were collected within 10 minutes of admission for all patients treated with rt-PA and promptly sent for analysis. The laboratory tests included measurements of albumin, blood urea nitrogen (BUN), creatinine, blood glucose, white blood cells (WBC), neutrophils, lymphocytes, neutrophil-to-lymphocyte ratio (NLR), monocytes, platelet (PLT), CRP, international normalized ratio (INR), and fibrinogen levels. (2) Patient demographic and clinical data were systematically collected, including gender, age, body mass index (BMI), smoking history, alcohol consumption history, disease history, medication history, onset-to-needle time (ONT), systolic blood pressure, diastolic blood pressure, TOAST classification, and record National Institute of Health Stroke Scale (NIHSS) scores measured before IVT, immediately after thrombolysis, 24 hours post-thrombolysis, 7 days post-thrombolysis, and at discharge. Modified Rankin Scale (mRS) scores were recorded before the current stroke onset and at discharge, 90-day functional outcomes were assessed through outpatient follow-up or telephone follow-up, with mRS scores used as a quantitative measure, defining scores of 0–1 as excellent outcomes and scores of 2–6 as poor outcomes. (3) Chest and cranial imaging data were collected during hospitalization. Routine cranial imaging was performed before IVT, 24–36 hours after IVT, and 7 days after IVT, with additional re-evaluations conducted if there were significant changes in the patient's condition.

Epicardial Adipose Tissue Volume Data Acquisition

All patients underwent chest CT scans during hospitalization. The CT scans were conducted using a General Electric Lightspeed CT (GE Medical Systems, Optima CT 620) scanners, with a slice thickness of 5mm and a slice interval of 5mm.

Two trained researchers analyzed each patient's EAT using Slice-O-Matic software (Tomovision), whose reliability for measuring adipose tissue has been demonstrated in previous studies.[14] Patients' chest CT images were saved as DICOM images and imported into Slice-O-Matic software for analysis. Based on established protocols, EAT was defined as tissue located within the pericardium and around the coronary arteries, extending from the level of the pulmonary artery trunk to the surface of the diaphragm, with attenuation ranging from -190 to -30 hounsfield units (HU).[15] The pericardial contour was manually traced every 5 mm to delineate EAT, and the software then automatically calculated the epicardial EATV and the average CT attenuation of EAT.

Hemorrhagic Transformation

Cranial CT or MRI was re-examined 24–36 hours after IVT or upon clinical deterioration to assess HT. According to European Cooperative Acute Stroke Study (ECASS) group, in ECASS II,[16] HT was categorized into hemorrhagic infarction (HI) and parenchymal hemorrhage (PH). According to hemorrhage volume and space-occupying effect, HT was further classified into HI1, HI2, PH1, PH2 and symptomatic intracranial hemorrhage (sICH) categories. HI1 was defined as small petechiae along the infarct edges; HI2 as confluent petechiae within the infarcted area without a space-occupying effect; PH1 as blood clots occupying 30% or less of the infarcted area with minimal space-occupying effect; and PH2 as blood clots occupying more than 30% of the infarcted area with substantial space-occupying effect. SICH was defined as intracranial hemorrhage at any site in the brain on the CT scan (as assessed by the CT reading panel, independently of the assessment by the investigator), documentation by the investigator of clinical deterioration, or adverse events, such as drowsiness, worsening hemiparesis or an increase in the NIHSS score by 4 points or more.

Statistical Analysis

Statistical analysis was conducted using SPSS 26.0 (IBM, Armonk, NY, United States). The Shapiro–Wilk assessed the normality of continuous variables. Normally distributed data were described using mean±standard deviation (SD), independent *t*-test was used for inter-group comparisons; Skewed data were described using median (interquartile range), with the Wilcoxon Mann–Whitney test used for inter-group comparisons. Categorical variables were described using counts (percentages), and the chi-square test or Fisher's exact test was used for inter-group comparisons. Univariate logistic regression analysis was initially performed to investigate the relationships between EAT, HT, PH, and 90-day outcome. Factors with $p < 0.05$ in univariate analysis were included in the multivariate logistic regression analysis. EATV was categorized by quartiles for multivariate logistic regression analysis related to HT, and included as a continuous variable for PH analysis. Receiver operating characteristics (ROC) curve were plotted to assess the predictive efficacy of EATV or EAT attenuation, with optimal cut-off values and corresponding sensitivity and specificity determined using the maximal Youden's Index. Spearman correlation analysis was employed to examine potential factors related to EATV and EAT attenuation. A bilateral $p < 0.05$ was considered statistically significant.

Results

A total of 328 patients with AIS received IVT during the study period, 62 patients were excluded and 36 patients incompleted the 90-day follow-up, 230 patients were included in the final analysis. Among these 230 patients, 52 (22.6%) developed with HT, of which 28 (12.2%) were classified as PH, and 10 (4.4%) as sICH, consistent with previous research findings.[17] 145 (63.0%) patients have an excellent 90-day functional outcome (Figure 1).

EAT with PH and HT

Baseline Information

The study stratified all patients based on the presence of HT or PH. A comparison of baseline characteristics is provided in Table 1.

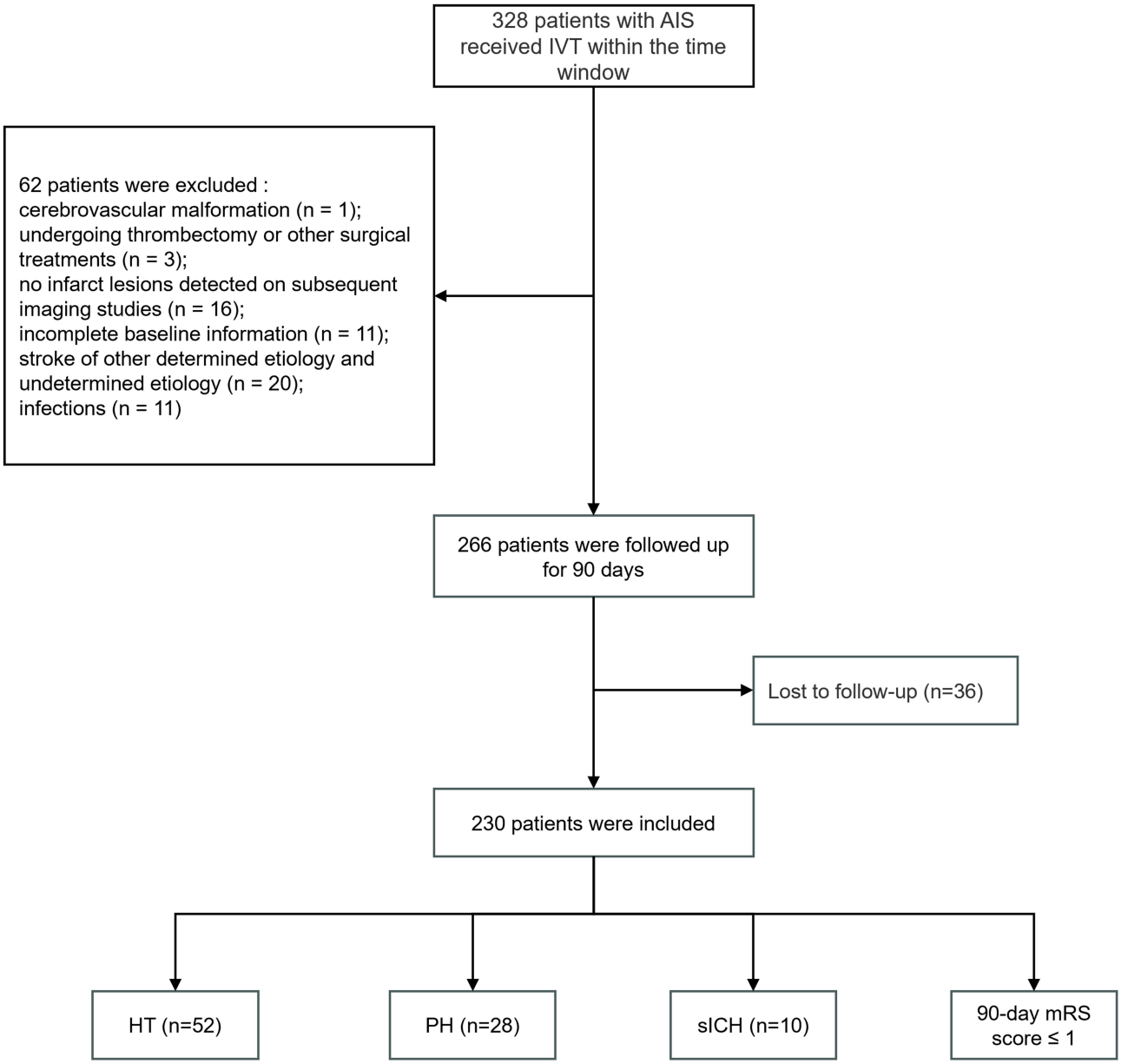

Figure 1 The flow chart of the study.
Abbreviations: AIS, acute ischemic stroke; IVT, intravenous thrombolysis; HT, hemorrhagic transformation; PH, parenchymal haemorrhage; sICH, symptomatic intracranial haemorrhage; mRS, modified Rankin Scale.

The average age of the 230 patients was 65.88 ± 11.79 years, with 152 (66.1%) males. The median ONT was 163.00 (112.75, 204.25) minutes, the median NIHSS score before IVT was 5.50 (3.00, 10.00), the median EATV was 98.43 (77.38, 120.33) cm^3, the mean EAT attenuation was −75.58 ± 3.75 HU.

Comparisons between groups showed that compared to non-HT patients, those with HT had a larger EATV (112.65 [97.33, 135.80] cm^3 vs 92.32 [72.74, 115.80] cm^3, $p < 0.001$) and higher EAT attenuation (−73.82 ± 3.76 HU vs −76.10 ± 3.60 HU, $p < 0.001$). Similarly, compared to non-PH patients, those with PH had a larger EATV (115.29 [98.21, 135.80] cm^3 vs 96.75 [76.34, 118.10] cm^3, $p = 0.001$) and higher EAT attenuation (−73.91 ± 4.17 HU vs −75.81 ± 3.64 HU, $p = 0.012$) (Supplementary Figures 1 and 2). Significant differences in TOAST classification were observed between HT and non-HT patients and between PH and non-PH patients ($p < 0.001$). HT and PH patients also had higher ages, pre-thrombolysis NIHSS scores, NLR, CRP levels, and prevalence of atrial fibrillation, and lower levels of albumin, lymphocyte, and PLT (all $p < 0.05$). Additionally, HT patients have a higher prevalence of diabetes compared

Table 1 Demographic and Clinical Characteristics of Patients, Stratified by the Presence of HT, PH

Variables	Total (n = 230)	HT (n = 52)	Non – HT (n = 178)	p	PH (n = 28)	Non – PH (n = 202)	p
Age (years), mean±SD	65.88±11.79	69.52±10.63	64.81±11.93	0.011*	70.04±10.92	65.30±11.82	0.046*
Male, (n, %)	152 (66.1%)	31 (59.6%)	121 (68.0%)	0.262	15 (53.6%)	137 (67.8%)	0.136
ONT (min), median (M25, M75)	163.00 (112.75, 204.25)	155.00 (117.00, 185.00)	164.00 (111.75, 208.50)	0.854	152.50 (92.00, 183.75)	164.00 (113.75, 206.50)	0.456
EATV (cm^3), median (M25, M75)	98.43 (77.38, 120.33)	112.65 (97.33, 135.80)	92.32 (72.74, 115.80)	<0.001*	115.29 (98.21, 135.80)	96.75 (76.34, 118.10)	0.001*
EAT attenuation (HU), mean±SD	−75.58±3.75	−73.82±3.76	−76.10±3.60	<0.001*	−73.91±4.17	− 75.81±3.64	0.012*
BMI (Kg/m^2), mean±SD	24.47±3.62	24.17±3.60	24.55±3.63	0.509	24.12±3.87	24.51±3.59	0.588
Systolic blood pressure (mmHg), mean±SD	151.76±19.91	149.27±18.97	152.49±20.18	0.306	150.39±21.20	151.95±19.78	0.699
Diastolic blood pressure (mmHg), mean±SD	85.91±13.73	86.19±13.59	85.83±13.81	0.866	83.25±14.51	86.28±13.62	0.275
mRS score before onset, median (M25, M75)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.907	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.341
NIHSS score before IVT, median (M25, M75)	5.50 (3.00, 10.00)	11.00 (6.00, 14.75)	4.00 (2.00, 8.00)	<0.001*	12.00 (7.75, 16.00)	5.00 (2.75, 8.00)	<0.001*
TOAST, (n, %)				<0.001*			<0.001*
SAA	140 (60.9%)	8 (15.4%)	132 (74.2%)		3 (10.7%)	137 (67.8%)	
LAA	63 (27.4%)	22 (42.3%)	41 (23.0%)		15 (53.6%)	48 (23.8%)	
CE	27 (11.7%)	22 (42.3%)	5 (2.8%)		10 (35.7%)	17 (8.4%)	
Risk factors, (n, %)							
Hypertension	144 (62.6%)	32 (61.5%)	112 (62.9%)	0.856	16 (57.1%)	128 (63.4%)	0.524
Diabetes mellitus	52 (22.6%)	19 (36.5%)	33 (18.5%)	0.006	9 (32.1%)	43 (21.3%)	0.198
Coronary artery disease	39 (17.0%)	10 (19.2%)	29 (16.3%)	0.619	3 (10.7%)	36 (17.8%)	0.502
Atrial fibrillation	38 (16.5%)	24 (46.2%)	14 (7.9%)	<0.001*	11 (39.3%)	27 (13.4%)	0.001*
Stroke	42 (18.3%)	7 (13.5%)	35 (19.7%)	0.309	4 (14.3%)	38 (18.8%)	0.561
Smoking history	78 (33.9%)	12 (23.1%)	66 (37.1%)	0.061	6 (21.4%)	72 (35.6%)	0.136
Alcohol history	61 (26.5%)	10 (19.2%)	51 (28.7%)	0.176	4 (14.3%)	57 (28.2%)	0.118
Medication history, (n, %)							
Antiplatelets	20 (8.7%)	4 (7.7%)	16 (9.0%)	0.990	2 (7.1%)	18 (8.9%)	1.000
Statins	10 (4.3%)	1 (1.9%)	9 (5.1%)	0.556	1 (3.6%)	9 (4.5%)	1.000
Anticoagulants	5 (2.2%)	3 (5.8%)	2 (1.1%)	0.139	2 (7.1%)	3 (1.5%)	0.113
Antihypertensive	61 (26.5%)	12 (23.1%)	49 (27.5%)	0.552	4 (14.3%)	57 (28.2%)	0.118
Antidiabetic	31 (13.5%)	10 (19.2%)	21 (11.8%)	0.167	5 (17.9%)	26 (12.9%)	0.668
Laboratory tests before IVT							
Blood glucose (mmol/L), median (M25, M75)	7.36 (6.23, 9.24)	8.11 (6.68, 11.47)	7.14 (6.21, 9.02)	0.054	8.11 (6.78, 9.77)	7.18 (6.21, 9.20)	0.103
BUN (mmol/L), median (M25, M75)	6.29 (5.37, 7.60)	6.66 (5.80, 7.56)	6.16 (5.34, 7.60)	0.224	6.80 (5.18, 8.18)	6.22 (5.37, 7.43)	0.366
Creatinine (μmol/L), median (M25, M75)	66.30 (56.05, 77.93)	63.98 (55.78, 80.35)	66.45 (57.15, 77.40)	0.751	63.93 (54.88, 84.64)	66.30 (56.32, 77.34)	0.881
Albumin (g/L), median (M25, M75)	43.78 (41.45, 45.82)	42.04 (38.96, 43.94)	44.36 (42.31, 46.35)	<0.001*	42.36 (39.17, 44.22)	43.96 (41.73, 46.29)	0.002*

(*Continued*)

https://doi.org/10.2147/JIR.S499351

Table 1 (Continued).

Variables	Total (n = 230)	HT (n = 52)	Non – HT (n = 178)	p	PH (n = 28)	Non – PH (n = 202)	p
WBC (10^9/L), median (M25, M75)	7.25 (6.05, 8.93)	7.23 (5.76, 9.43)	7.26 (6.16, 8.75)	0.964	7.77 (6.41, 9.54)	7.24 (5.95, 8.77)	0.280
Neutrophil (10^9/L), median (M25, M75)	4.53 (3.41, 5.99)	4.52 (3.43, 6.54)	4.53 (3.37, 5.85)	0.466	5.70 (4.00, 6.87)	4.49 (3.34, 5.85)	0.039*
Lymphocyte (10^9/L), median (M25, M75)	1.89 (1.52, 2.51)	1.61 (1.26, 2.10)	1.98 (1.61, 2.58)	0.002*	1.60 (1.26, 1.98)	1.95 (1.55, 2.55)	0.019*
NLR, median (M25, M75)	2.29 (1.66, 3.34)	2.61 (2.15, 4.05)	2.17 (1.60, 3.09)	0.008*	2.98 (2.20, 4.62)	2.22 (1.61, 3.21)	0.005*
Monocyte (10^9/L), median (M25, M75)	0.49 (0.40, 0.61)	0.48 (0.36, 0.60)	0.49 (0.42, 0.62)	0.416	0.48 (0.39, 0.56)	0.49 (0.41, 0.62)	0.791
PLT (10^{12}/L), median (M25, M75)	204.00 (175.00, 237.25)	177.50 (151.25, 207.00)	213.50 (183.75, 242.25)	<0.001*	178.50 (152.25, 228.75)	209.50 (178.00, 238.25)	0.026*
CRP (mg/L), median (M25, M75)	0.58 (0.00, 1.58)	1.31 (0.58, 2.58)	0.00 (0.00, 1.35)	<0.001*	1.21 (0.00, 3.55)	0.53 (0.00, 1.44)	0.016*
INR (10^9/L), median (M25, M75)	1.09 (1.03, 1.14)	1.08 (1.02, 1.17)	1.09 (1.04, 1.13)	0.875	1.09 (1.02, 1.17)	1.09 (1.04, 1.14)	0.878
Fibrinogen (g/L), median (M25, M75)	2.79 (2.46, 3.20)	2.97 (2.48, 3.43)	2.77 (2.43, 3.14)	0.072	2.88 (2.47, 3.41)	2.79 (2.44, 3.20)	0.402

Note: "*" means statistically significant differences ($p < 0.05$).

Abbreviations: HT, hemorrhagic transformation; PH, parenchymal haemorrhage; ONT, onset-to-needle time; EATV, epicardial adipose tissue volume; EAT,epicardial adipose tissue; BMI, body mass index; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; IVT, intravenous thrombolysis; TOAST, Trial of Org 10172 in Acute Stroke Treatment; SAA, small-vessel occlusion; LAA, large-artery atherosclerosis; CE, cardioembolism; BUN, blood urea nitrogen; WBC, white blood cells; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet; CRP, C-reactive protein; INR, international normalized ratio. p, significance of comparative analysis.

to the non-HT patients (36.5% vs 18.5%, p = 0.006), and PH patients have higher neutrophil levels compared to the non-PH patients (5.70 [4.00, 6.87] vs 4.49 [3.34, 5.85], p = 0.039).

Logistic Regression Analysis

The results of univariate logistic regression analysis for HT and PH were shown in Supplementary Table 1. Factors with p < 0.05 in the univariate analysis were further included in the multivariate logistic regression analysis (Figure 2 and Table 2).

After adjusting for potential confounding factors, EATV levels, categorized by quartiles, was identified as an independent risk factor for HT (p = 0.029). Specifically, compared to the first quartile of EATV, the third quartile (OR 9.254, 95% CI 1.533–55.853, p = 0.015) and fourth quartile (OR 11.117, 95% CI 1.925–64.211, p = 0.007) of EATV were associated with an increased risk of HT. In contrast, EAT attenuation was not an independent risk factor for HT (p = 0.378). Additionally, higher NIHSS score before IVT (OR 1.081, 95% CI 1.003–1.166, p = 0.041), elevated blood glucose levels on admission (OR 1.225, 95% CI 1.015–1.480, p = 0.035), and presence of atrial fibrillation (AF) (OR 6.803, 95% CI 1.593–29.062, p = 0.007) were identified as independent risk factors for HT, whereas higher albumin levels (OR 0.813, 95% CI 0.689–0.959, p = 0.014) were protective factors. From an etiological perspective, AIS patients with large-artery atherosclerosis (LAA) (OR 10.322, 95% CI 3.435–31.010, p < 0.001) or cardioembolism (CE) (OR 36.014, 95% CI 7.135–181.774, p < 0.001) had a higher risk of HT compared to those with small-vessel occlusion (SAA) (Figure 2 and Table 2).

EAT and 90-Day Functional Outcomes

All patients were grouped according to their 90-day mRS scores, and the baseline characteristics comparison results were presented in Table 3.

In patients with poor 90-day outcomes, EAT attenuation was higher compared to those with excellent 90-day outcomes (−73.87 ± 3.46 HU vs −76.58 ± 3.56 HU, p < 0.001). However, there was no significant difference in EATV between the two groups (99.90 [79.99, 128.65] cm^3 vs 97.66 [76.62, 117.40] cm^3, p = 0.236) (Table 3 and Supplementary Figure 3). The group with poor outcomes was characterized by older age, higher NIHSS score before IVT, higher INR levels, and lower levels of AST, albumin, and PLT (all p < 0.05). Significant differences were also noted between the groups in TOAST classification (p = 0.001). Additionally, a higher proportion of patients with AF was observed in the poor outcome group (25.9% vs 11.0%, p = 0.003) (Table 3).

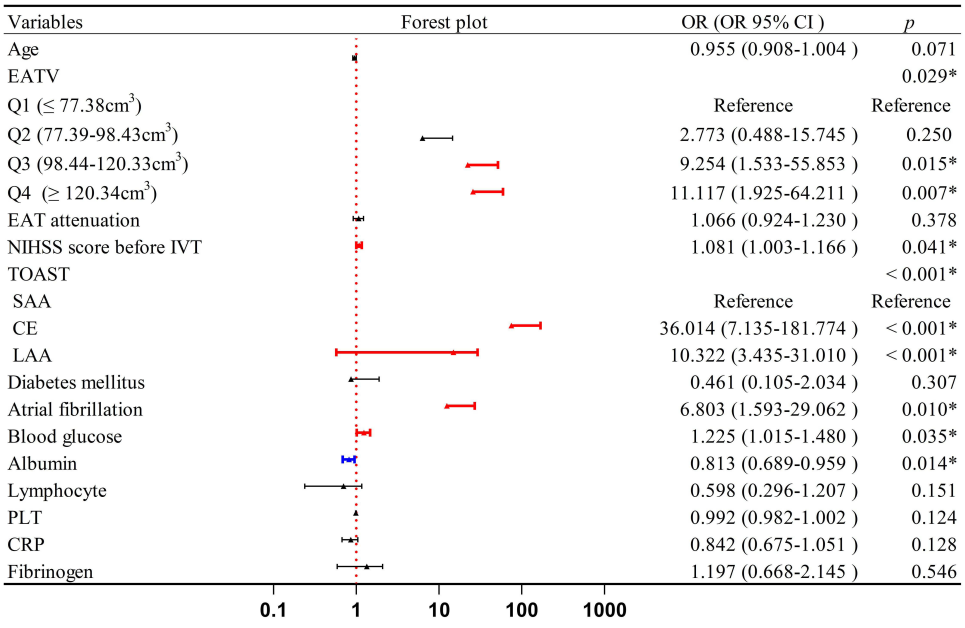

Figure 2 Multivariate logistic regression analysis and forest plot related to HT.
Note: "*" means statistically significant differences (p < 0.05).

https://doi.org/10.2147/JIR.S499351

Table 2 Logistic Regression Analysis to Identify Associations of EAT with PH

Variables	Crude Model		Adjusted Model	
	OR (OR 95% CI)	*p*	OR (OR 95% CI)	*p*
EATV	1.020 (1.008–1.032)	0.001*	1.022 (1.005–1.040)	0.013*
EAT attenuation	1.150 (1.030–1.284)	0.013*	1.050 (0.894–1.234)	0.554

Notes: "*" means statistically significant differences ($p < 0.05$). Adjust for age, EATV, EAT attenuation, NIHSS score before IVT, TOAST, atrial fibrillation, albumin, NLR, CRP.

Abbreviations: PH, parenchymal haemorrhage; EATV, epicardial adipose tissue volume; EAT, epicardial adipose tissue; NIHSS, National Institute of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein. p, significance of comparative analysis.

Table 3 Demographic and Clinical Characteristics of Patients, Stratified by 90-Day mRS

Variables	Total (n = 230)	90-Day mRS 0–1 (n = 145)	90-Day mRS 2–6 (n = 85)	*p*
Age (years), (M25, M75)	65.50 (58.00, 74.25)	65.00 (58.00, 72.00)	69.00 (61.50, 78.00)	0.010*
Male (n, %)	152 (66.1%)	101 (69.7%)	51 (60.0%)	0.135
ONT (min), median (M25, M75)	163.00 (112.75, 204.25)	165.00 (120.00, 205.00)	150.00 (92.50, 202.00)	0.295
EATV (cm^3), median (M25, M75)	98.43 (77.38, 120.33)	97.66 (76.62, 117.40)	99.90 (79.99, 128.65)	0.236
EAT attenuation (HU), mean±SD	−75.58±3.75	−76.58±3.56	−73.87±3.46	< 0.001*
BMI (Kg/m^2), mean±SD	24.47±3.62	24.62±3.40	24.20±3.97	0.402
Systolic blood pressure (mmHg), mean±SD	151.76±19.91	150.43±17.60	154.04±23.29	0.219
Diastolic blood pressure (mmHg), mean±SD	85.91±13.73	86.69±12.55	84.58±15.53	0.288
mRS score before onset, median (M25, M75)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.114
NIHSS score before IVT, median (M25, M75)	5.50 (3.00, 10.00)	4.00 (2.00, 7.00)	10.00 (6.00, 14.00)	< 0.001*
TOAST, (n, %)				0.001*
SAA	140 (60.9%)	99 (68.3%)	41 (48.2%)	
LAA	63 (27.4%)	37 (25.5%)	26 (30.6%)	
CE	27 (11.7%)	9 (6.2%)	18 (21.2%)	
Risk factors, (n, %)				
Hypertension	144 (62.6%)	90 (62.1%)	54 (63.5%)	0.825
Diabetes mellitus	52 (22.6%)	34 (23.4%)	18 (21.2%)	0.691
Coronary artery disease	39 (17.0%)	26 (17.9%)	13 (15.3%)	0.607
Atrial fibrillation	38 (16.5%)	16 (11.0%)	22 (25.9%)	0.003*
Stroke	42 (18.3%)	23 (15.9%)	19 (22.4%)	0.219
Smoking history	78 (33.9%)	57 (39.3%)	21 (24.7%)	0.024*
Alcohol history	61 (26.5%)	46 (31.7%)	15 (17.6%)	0.020*
Medication history, (n, %)				
Antiplatelets	20(8.7%)	15 (10.3%)	5 (5.9%)	0.246
Statins	10(4.3%)	7 (4.8%)	3 (3.5%)	0.896
Anticoagulants	5(2.2%)	3 (2.1%)	2 (2.4%)	1.000
Antihypertensive	61(26.5%)	44 (30.3%)	17 (20.0%)	0.086
Antidiabetic	31(13.5%)	21 (14.5%)	10 (11.8%)	0.560
Laboratory tests before IVT				
Blood glucose (mmol/L), median (M25, M75)	7.36 (6.23, 9.24)	7.20 (6.20, 9.10)	7.66 (6.36, 9.83)	0.401
BUN (mmol/L), median (M25, M75)	6.29 (5.37, 7.60)	6.21 (5.31, 7.29)	6.48 (5.47, 8.24)	0.119
Creatinine (μmol/L), median (M25, M75)	66.30 (56.05, 77.93)	65.90 (55.65, 78.65)	67.80 (57.30, 76.83)	0.593
Albumin (g/L), median (M25, M75)	43.78 (41.45, 45.82)	44.25 (42.55, 46.34)	42.78 (39.35, 45.35)	< 0.001*
WBC (10^9/L), median (M25, M75)	7.25 (6.05, 8.93)	7.40 (6.03, 8.96)	7.18 (6.05, 8.89)	0.670
Neutrophil (10^9/L), median (M25, M75)	4.53 (3.41, 5.99)	4.57 (3.36, 6.15)	4.48 (3.43, 5.82)	0.975

(*Continued*)

Table 3 (Continued).

Variables	Total (n = 230)	90-Day mRS 0–1 (n = 145)	90-Day mRS 2–6 (n = 85)	*p*
Lymphocyte (10^9/L), median (M25, M75)	1.89 (1.52, 2.51)	2.00 (1.55, 2.58)	1.79 (1.43, 2.26)	0.073
NLR, median (M25, M75)	2.29 (1.66, 3.34)	2.22 (1.60, 3.32)	2.32 (1.71, 3.35)	0.256
Monocyte (10^9/L), median (M25, M75)	0.49 (0.40, 0.61)	0.49 (0.42, 0.62)	0.48 (0.40, 0.60)	0.541
PLT (10^{12}/L), median (M25, M75)	204.00 (175.00, 237.25)	213.00 (183.00, 244.50)	192.00 (161.50, 227.00)	0.005*
CRP (mg/L), median (M25, M75)	0.58 (0.00, 1.58)	0.21 (0.00, 1.36)	0.98 (0.00, 1.96)	0.060
INR (10^9/L), median (M25, M75)	1.09 (1.03, 1.14)	1.08 (1.03, 1.13)	1.10 (1.05, 1.17)	0.022*
Fibrinogen (g/L), median (M25, M75)	2.79 (2.46, 3.20)	2.75 (2.43, 3.20)	2.82 (2.47, 3.25)	0.416

Note: "*" means statistically significant differences ($p < 0.05$).
Abbreviations: HT, hemorrhagic transformation; PH, parenchymal haemorrhage; ONT, onset-to-needle time; EATV, epicardial adipose tissue volume; EAT,epicardial adipose tissue; BMI, body mass index; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; IVT, intravenous thrombolysis; TOAST, Trial of Org 10172 in Acute Stroke Treatment; SAA, small-vessel occlusion; LAA, large-artery atherosclerosis; CE, cardioembolism; BUN, blood urea nitrogen; WBC, white blood cells; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet; CRP, C-reactive protein; INR, international normalized ratio. p, significance of comparative analysis.

The results of the univariate logistic regression analysis related to 90-day outcome are presented in Supplementary Table 2. Factors with $p < 0.05$ in the univariate analysis were further included in the multivariate logistic regression analysis (Table 4).

The results indicated that EAT attenuation (OR 1.170, 95% CI 1.056–1.297, $p = 0.003$) and NIHSS score before IVT (OR 1.152, 95% CI 1.072–1.238, $p < 0.001$) were independent risk factors for poor 90-day outcomes (Table 4).

Predict Models

The following ROC curves were plotted to evaluate predictive performance based on the above results (Figure 3).

According to the above results, the area under the curve (AUC) for EATV predicted HT was 0.705 (95% CI 0.632–0.778), with an optimal cutoff of 96.83 cm^3, sensitivity of 80.8%, and specificity of 45.5%. For predicting PH with EATV, the AUC was 0.693 (95% CI 0.597–0.789), with an optimal cutoff of 110.05 cm^3, sensitivity of 64.3%, and specificity of 30.7%. The AUC for predicting poor 90-day outcomes based on the EAT attenuation was 0.720 (95% CI 0.653–0.787), with an optimal cutoff of −76.35 HU, sensitivity of 80.0%, and specificity of 44.8%.

Table 4 Multivariate Logistic Regression Analysis of Risk Factors for 90-Day Functional Outcome

Variables	OR (OR 95% CI)	*p*
Age	1.019 (0.987–1.051)	0.255
EAT attenuation	1.170 (1.056–1.297)	0.003*
mRS score before onset	1.317 (0.900–1.926)	0.156
NIHSS score before IVT	1.152 (1.072–1.238)	< 0.001*
TOAST		0.613
SAA	Reference	Reference
CE	1.631 (0.528–5.039)	0.395
LAA	1.311 (0.621–2.768)	0.478
Atrial fibrillation	0.882 (0.332–2.347)	0.802
Albumin	0.963 (0.875–1.060)	0.442
PLT	0.997 (0.991–1.004)	0.382
INR	2.558 (0.089–73.661)	0.584

Note: "*" means statistically significant differences ($p < 0.05$).
Abbreviations: EAT, epicardial adipose tissue; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; IVT, intravenous thrombolysis; TOAST, Trial of Org 10172 in Acute Stroke Treatment; PLT, platelet; INR, international normalized ratio. p, significance of comparative analysis.

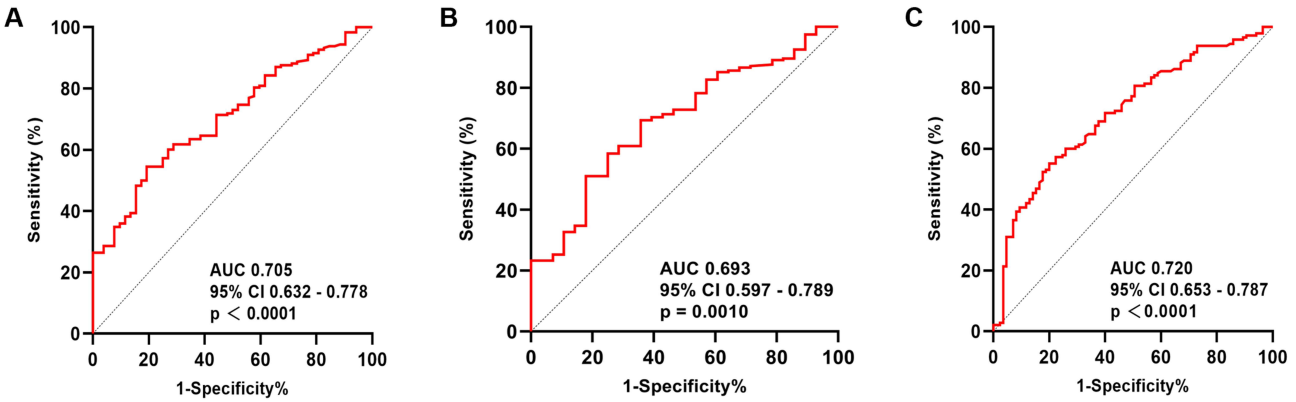

Figure 3 ROC curves. (**A**) shows ROC curve of EATV and HT, the AUC for EATV predicted HT was 0.705 (95% CI 0.632–0.778). (**B**) shows ROC curve of EATV and PH, the AUC was 0.693 (95% CI 0.597–0.789). (**C**) shows ROC curve of EAT attenuation and 90-day mRS 2–6, the AUC was 0.720 (95% CI 0.653–0.787).

Correlation Analysis

The correlation analysis of EATV and EAT attenuation is detailed in Table 5.

Additional independent risk factors and inflammatory markers associated with HT and poor 90-day outcomes were included in the correlation analysis with EATV or EAT attenuation. The study found that EATV was positively correlated with AF ($r = 0.216$, $p < 0.001$), blood glucose ($r = 0.151$, $p = 0.022$), and CRP ($r = 0.209$, $p = 0.001$). EAT attenuation was positively correlated with NIHSS score before IVT ($r = 0.342$, $p < 0.001$) and CRP ($r = 0.157$, $p = 0.017$), and negatively correlated with lymphocytes ($r = -0.174$, $p = 0.008$) (Table 5).

Discussion

This retrospective study assessed the risk factors for HT in AIS patients following IVT. (1) Consistent with prior research, the study confirmed that higher NIHSS score before IVT, elevated blood glucose levels, presence of AF, and lower albumin levels are independent risk factors for HT. In terms of etiological classification, patients with CE and LAA subtypes showed a greater likelihood for developing HT compared to those with SAA. (2) Additionally, the study revealed a significant association between EAT and both HT and 90-day outcomes. Patients with HT or PH exhibited higher EATV and EAT attenuation compared to those without HT and PH. Multivariable logistic regression analysis

Table 5 Correlation Analysis Between EATV and EAT Attenuation

Variables	EATV		EAT Attenuation	
	r	*p*	*r*	*p*
NIHSS score before IVT	0.064	0.331	0.342	< 0.001*
Atrial fibrillation	0.216	< 0.001*		
Blood glucose	0.151	0.022*		
Albumin	0.033	0.621		
WBC	− 0.058	0.383	− 0.037	0.581
Neutrophil	− 0.059	0.374	− 0.009	0.888
Lymphocyte	− 0.025	0.711	− 0.174	0.008*
NLR	− 0.032	0.624	0.119	0.072
Monocyte	− 0.060	0.368	− 0.009	0.897
CRP	0.209	0.001*	0.157	0.017*

Note: "*" means statistically significant differences ($p < 0.05$).

Abbreviations: EATV, epicardial adipose tissue volume; EAT, epicardial adipose tissue; NIHSS, National Institute of Health Stroke Scale; IVT, intravenous thrombolysis; WBC, white blood cells; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; r, correlation coefficient; p, significance of comparative analysis.

indicated that higher EATV was an independent predictor for HT and PH. Moreover, patients with poor 90-day outcomes had significantly higher EAT attenuation. ROC curves demonstrated that EAT showed high sensitivity for predicting HT and poor 90-day outcomes, suggesting that EAT may be valuable in identifying high-risk individuals for HT and adverse prognoses. However, the low specificity of EAT implied that it could potentially overestimate the risks of HT and poor outcomes. (3) Correlation analysis further revealed that EATV was positively correlated with AF, elevated blood glucose, and higher CRP levels, while EAT attenuation was positively associated with NIHSS score before IVT and CRP, and negatively correlated with lymphocyte levels.

Our study findings corroborates with previous research indicating that higher NIHSS score before IVT, elevated blood glucose levels, presence of AF, and lower albumin levels are independent risk factors for HT. Additionally, among different stroke types, we observed that patients with CE and LAA subtypes of stroke are at greater risk for HT compared to those with SAA.[18,19] Elevated NIHSS score reflect more severe ischemia and extensive tissue damage.[20] Although glucose serves as the primary energy source for brain cells,[21] early stress hyperglycemia in stroke may initially exert a protective effect on brain tissue.[22] However, following reperfusion, elevated blood glucose levels can activate NADPH oxidase, leading to increased oxidative stress, blood-brain barrier (BBB) disruption, and heightened risk of HT.[23] Research indicates that albumin may help maintain BBB integrity through its anti-inflammatory, antioxidant, and anti-endothelial damage properties,[24] and malnutrition can elevate the risk of HT and worsen outcomes after IVT.[25] Previous studies have shown that patients with SAA have a reduced risk of HT,[26] while those with AF benefit less from IVT.[27] Research on atherosclerosis has shown that carotid artery calcification correlates with HT and adverse outcomes post-thrombolysis.[28] HT is associated with ischemia-reperfusion injury, coagulation abnormalities, and BBB disruption, with inflammation-mediated BBB disruption playing a pivotal role.[29,30] Treatment with rt-PA significantly increases the risk of HT due to its cytotoxic effects,[31] which heighten BBB permeability and trigger neuroinflammation, exacerbating BBB disruption.[29,32] Autopsy findings from AIS patients with HT revealed higher levels of neutrophil infiltration and Matrix metalloproteinase-9 (MMP-9) at hemorrhagic sites,[33] underscoring the critical role of rt-PA-induced neutrophil-derived MMP-9 in HT.[34] Furthermore, patients with HT and PH exhibited elevated baseline levels of NLR and CRP, with PH patients showing significantly elevated neutrophil counts.

EAT is a metabolically active tissue that can produce pro-atherogenic and pro-inflammatory factors, such as Interleukin-1beta (IL-1β), Interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1) under chronic inflammatory conditions like obesity.[35] Due to its proximity to cardiomyocytes and coronary arteries, these factors can be released into adjacent tissues and the bloodstream through paracrine and vascular secretion,[36] contributing to the development of coronary artery disease, heart failure, AF, atherosclerosis, and AIS.[37–39] Our study is the first to confirm that higher EATV is an independent risk factor for HT and PH in AIS patients after IVT. We also found a positive correlation between CRP levels and EATV, suggesting that inflammation as a potential underlying mechanism. Previous research has also shown a significant association between EATV and inflammatory factors.[40] Researchers observed elevated levels of IL-1β, IL-6, MCP-1, and TNF-α in human EAT, and individuals with higher EATV also exhibited increased expression of CRP, IL-6, and MCP-1 in circulation.[41] These factors can recruit inflammatory cells, promote MMP-9 expression in a dose-dependent manner, induce endothelial cell activation, and elevate the risk of bleeding.[42] Studies have identified systemic inflammation markers and inflammatory factors as significant risk factors for HT.[42–45] Some studies posit that inflammatory mediators produced by EAT can impact blood vessels, contributing to both atherosclerosis and endothelial dysfunction.[46] EATV may be valuable for early detection of vascular dysfunction.[47]

The secretion of pro-inflammatory and pro-fibrotic factors by EAT may lead to cardiac structural remodeling and dysfunction, potentially triggering AF.[48,49] Prior research has demonstrated that individuals with AF have a 3- to 5-fold increased risk of AIS compared to those without AF.[50] AF-related ischemic events often result in larger infarct areas and a higher risk of HT due to larger emboli and inadequate collateral circulation.[51] Our study further supported that AF was an independent risk factor for HT and showed that AF patients had higher EATV. Based on these findings, we hypothesized that EAT may contribute to the development of AF via secreting cytokines, which in turn may increase the incidence of HT.

EAT attenuation is emerging as a novel inflammatory marker for quantifying peripheral vascular inflammation.[10,15] Previous studies have demonstrated that higher EAT attenuation levels are predictive of atherosclerosis, adverse cardiovascular events, and metabolic syndrome, potentially due to the presence of more high-density pro-inflammatory factors in EAT.[52–54] These factors, originating from both EAT itself and nearby vascular paracrine, not only promote inflammation but also inhibit lipid formation within adipocytes.[10] Some researchers suggested that EAT attenuation reflect the lipid content and inflammation level within the tissue, with higher EAT attenuation potentially indicating a greater ratio of high-density pro-inflammatory factors to low-density adipose tissue components.[53] Alternatively, other researchers proposed that the activation of EAT metabolism could lead to an increase in EAT attenuation.[55] Our study aligns with previous research, as it found that mortality risk and poor prognosis was specifically associated with EAT attenuation, whereas EATV has not shown the same predictive value.[56,57] EAT attenuation was identified as a distinct marker of vascular inflammation, separate from EATV.[58] Furthermore, patients on statin therapy have demonstrated a significant reduction in EAT attenuation, which aligns with previous research, it may be related to other beneficial mechanisms of action of statin.[59,60] Therefore, further investigation into the impact of statin on EAT and their mechanism of action is warranted in future studies.

Additionally, we found that only the NIHSS score before IVT and EAT attenuation were independent risk factors for poor prognosis after IVT. In addition to the increasing trend of NLR in the population with poor prognosis, other inflammatory cells detected at admission had no predictive value for prognosis. Studies have demonstrated that the inflammatory cascade induced by AIS exhibits a time-dependent effect, characterized by a rapid increase in neutrophils and the NLR during the acute phase (6–48 hours), peaking between 12 and 48 hours.[61,62] Perhaps because our blood samples were collected in the hyperacute phase of AIS (within 6 hours), they failed to reflect the predictive value of inflammatory cells for prognosis. Previous research has also indicated that leukocyte levels, neutrophil counts, and NLR within 24 hours following IVT are positively correlated with HT and poor prognosis, whereas pre-IVT indicators do not show such correlations.[63] In addition, we were unable to determine the relationship between EATV and prognosis in patients with IVT, and further studies are needed in the future.

This study still has several limitations. First, the sample size was relatively small, necessitating multicenter studies with larger cohorts to further validate the differences in EATV and EAT attenuation among patients with varying degrees of HT (Supplementary Figures 2 and 3). Second, incorporating additional relevant indicators could enhance the predictive accuracy of EAT for HT and prognosis. Lastly, further research is required to investigate the pathological mechanisms underlying EAT, including the detection of additional inflammatory factors. In addition, since the purpose of our experiment was to use the data before IVT to identify the risk factors that can predict HT after IVT, the analysis of the dynamic changes of blood indicators after IVT was neglected. The trend of blood changes before and after IVT needs to be further studied in future trials.

Conclusion

This study is the first to elucidate the relationship between EAT and HT, as well as functional outcomes in AIS patients who received IVT. The research reveal that higher EATV is an independent risk factor for HT and PH. Additionally, higher EAT attenuation can predict poor outcome at 90 days, indicating that EAT holds substantial predictive value for HT and long-term prognosis. Quantifying EAT using chest CT offers greater accuracy than using echocardiography, and is less affected by the timing of AIS onset, making it a valuable tool for early screening of high-risk patients for HT following IVT. Future research should focus on controlling EAT inflammation, although additional studies are necessary to further investigate the clinical significance and underlying mechanisms of EAT.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding authors upon request.

Ethical Approval

This retrospective review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 helsinki Declaration and its later amendments or

comparable ethical standards. The Ethics Committee of Affiliated Hospital of Qingdao University approved this study. Given the retrospective nature of the study, the requirement for consent was waived in accordance with the approval of the Ethics Committee. The data of all participants was anonymized and maintained in strict confidence.

Acknowledgments

This work was supported by the National Natural Science Foundation of China [grant numbers: 81971111, 82371331].

Disclosure

The authors report no conflicts of interest in this work.

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