

ARTICLE

Association of concomitant headache with hypoperfusion in ischemic stroke: A multimodal CT-based study

Yi Ge | Wanli Dong | Haifeng Lu | Ximeng Zhang | Shicun Huang | Yi Yang  | Jianqiang Ni

Department of Neurology, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China

Correspondence

Yi Yang and Jianqiang Ni, Department of Neurology, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215000, China.
Email: 13656229395@163.com and njq@suda.edu.cn

Abstract

Previous investigations indicate that vessel wall elasticity may contribute to the occurrence of an ischemic stroke-associated headache. In this prospective study, the association between radiologic parameters of intracranial hemodynamic changes and concomitant headaches during the early phase of ischemic stroke was examined. Consecutive patients with acute ischemic stroke (AIS) from the First Affiliated Hospital of Soochow University were recruited and divided into two groups according to their questionnaire results and the International Classification of Headache Disorder 3 criteria. Baseline data, including stroke subtypes and neurological function, at admission and discharge were collected. Non-contrast computed tomography (CT), CT angiography, and CT perfusion were performed to assess intracranial hemodynamic changes. Multiple adjusted logistic models were used and possible confounding factors were included in sequential models. A total of 190 patients with AIS (93 headaches and 97 non-headache) were recruited. There were significant differences between the two groups in gender, hypertension, Alberta stroke program early CT score, relative cerebral blood flow (rCBF), and relative cerebral blood volume (rCBV). Furthermore, rCBV (adjusted odds ratio [OR] 0.160; 95% confidence interval [CI], 0.055–0.461; $p < 0.001$) and rCBF (adjusted OR, 0.309; 95% CI, 0.113–0.844; $p < 0.05$) were significantly associated with concomitant headache during the early phase of AIS in fully adjusted models. After adjusting for sociodemographic characteristics and other confounding factors, p values for the ORs were robust and intensified. Patients with lower rCBV and rCBF tended to experience the concomitant headache during the early phase of AIS. Regional hypoperfusion and microcirculation might play an important role in this separate clinical entity.

Abbreviations: ADL, Barthel index of Activities of Daily Living; AIS, acute ischemic stroke; ASPECTS, Alberta stroke program early CT score; CTA, CT angiography; CTP, CT perfusion; ICHD-3, International Headache criteria 3; IQR, interquartile range; IS, ischemic stroke; MRI, magnetic resonance imaging; NCCT, non-contrast CT; NIHSS, National Institutes of Health Stroke Scale; PC-ASPECTS, posterior circulation ASPECTS; rCBF, relative cerebral blood flow; rCBV, relative cerebral blood volume; rLMC, regional leptomeningeal collateral score; rMTT, relative mean transit time; rTTP, relative time to peak.; SDs, spreading depolarization; TOAST, Trial Org 10,172 in Acute Stroke Treatment.

Yi Ge and Wanli Dong contributed equally.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

The underlying mechanisms of concomitant headache during the early phase of ischemic stroke are still unknown. Previous investigations indicate that vessel wall elasticity may be a necessary contributing factor.

WHAT QUESTION DID THIS STUDY ADDRESS?

In this prospective study, the association between radiologic parameters of intracranial hemodynamic changes and concomitant headaches during the early phase of was examined to confirm our hypothesis that patients with regional hypoperfusion were expected to have more frequent headaches.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Patients with lower relative cerebral blood flow and relative cerebral blood volume tended to experience the concomitant headache during the early phase of acute ischemic stroke. Regional hypoperfusion and microcirculation might play an important role in this separate clinical entity.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Controls of regional hypoperfusion may be a potential target for future therapeutic interventions of the concomitant headache during the early phase of ischemic stroke.

INTRODUCTION

Ischemic stroke is frequently associated with concomitant headache and is more common in women, younger patients, and those without hypertension.¹⁻⁴ Most headaches had tension-type features, were moderate and became chronic in nature.¹ The overall incidence rate varied considerably among the studies, from 6% to 51%.^{1,5}

Accurate diagnosis of concomitant headache during the early phase of an ischemic stroke is of strategic importance to patients with acute ischemic stroke (AIS). However, atypical symptoms and uncertain temporal patterns of headache and stroke bring great challenges to diagnosis.¹ Meanwhile, the underlying mechanisms of headaches are still unknown, which may be due to increased susceptibility to spreading depolarizations (SDs) and changes in cerebral blood flow.^{3,6,7} Previous investigations indicate that vessel wall elasticity may be a necessary contributing factor in the occurrence of an ischemic stroke-associated headache.^{1,7} In addition, vessel wall elasticity is closely related to mean arterial pressure and tissue perfusion.⁸ Multimodal computed tomography (CT) allows assessment not only of the macrovascular vessels but also of the microcirculation, which can demonstrate changes at the tissue level. These radiologic characteristics may be helpful in the diagnosis of concomitant headache.⁹

In the present study, we proposed a hypothesis that patients with regional hypoperfusion were expected to more frequently have headaches associated with ischemic stroke. To test it, we performed non-contrast CT (NCCT),

CT angiography (CTA), and CT perfusion (CTP) to assess the association between intracranial hemodynamic changes and ischemic stroke-associated headache during the early phase of ischemic stroke.

MATERIALS AND METHODS

Study population

We analyzed prospectively collected data in consecutive patients (preliminary diagnosis is AIS) from January 2019 to December 2020 in the emergency stroke center of the First Affiliated Hospital of Soochow University (a level 3A hospital). Routine blood and biochemical tests and electrocardiogram (ECG) were performed for all patients at admission. All patients accepted the same imaging protocol and questionnaires prospectively in the stroke center. This study involving human participants was reviewed and approved by the Institutional Review Board of The First Affiliated Hospital of Soochow University. All patients gave written informed consent.

The initial sample included 475 patients. Exclusion criteria were as follows: (1) patients were younger than 18 years old; (2) patients with stroke caused by intracranial hemorrhage, subarachnoid hemorrhage, or sinus venous thrombosis; (3) patients with head trauma; (4) patients with intracranial infection or brain tumors; (5) patients with allergies, allergic aphasia, and/or unconsciousness; (6) patients with missing data (no multimodal

CT results within 48 h of admission or no complete questionnaire results); (7) patients were diagnosed with a transient ischemic attack during clinical follow-up; and (8) patients could not accurately distinguish whether there was a headache.

Only 190 patients with AIS were included and formed the basis of this report. All subjects received standardized medical advice and treatment according to the current guidelines. AIS cases were confirmed by magnetic resonance imaging. Patients were divided into headache group (HA+) or non-headache group (HA-) according to the questionnaire results and the International Classification of Headache Disorder 3 (ICHD-3) diagnostic criteria for headache attributed to ischemic stroke.¹⁰

Clinical information collection

Baseline data were collected, including demographic features, cerebral vascular risk factors, such as hypertension and diabetes, through electronic patient records and administrative databases. ECG examination was used for diagnosis of atrial fibrillation. Intracranial magnetic resonance angiography (MRA), extracranial carotid and vertebral artery MRA, or Doppler ultrasound were applied for vascular evaluation. We also assessed the following clinical characteristics: stroke subtypes based on Trial Org 10172 in Acute Stroke Treatment (TOAST) classification, neurological function at admission and discharge based on National Institutes of Health Stroke Scale (NIHSS), and the Barthel index of Activities of Daily Living (ADL).

Headache questionnaire

Headache characteristics were collected at admission and discharge by doctors with a semistructured questionnaire. Patients who answered “no” to question 1 were allocated into the HA- group. The questionnaire contained the following questions: (1) Did you have a headache during, or shortly before/after the ischemic stroke? (2) What exact time did the headache appear? (3) Can you describe your headache? (4) Did you have this type of headache before? (5) How long did the headache last? (6) Where were there any other symptoms.⁷

Radiologic parameters

All patients were scanned immediately when they presented to the emergency center. Additional informed consent was obtained in patients with NIHSS score <6. After a conventional CT scan and exclusion of cerebral

hemorrhage, CTA and CTP were performed (dual-source spiral CT, Siemens). For CTA, 50–80 ml non-ionic contrast medium (Omnipaque, 300 mg/ml) was injected into the antecubital vein (18-G needle) at a rate of 5 ml/s. Time-density curves were obtained and transferred to the image workstation (Syng. VIA) for processing by VPCT Neuro-STROKE. CTP images were post-processed using the MISTar software.

The infarct core and the surrounding penumbra were identified on the baseline CTP image; the largest dimension of the lesion was selected for measurement on the pseudo-color map of perfusion parameters; the region of interest was outlined manually according to the distribution of blood supply to the cerebral arteries and the junctional area; the perfusion parameters were measured on the affected side and the corresponding zone on the healthy side (relative cerebral blood flow [rCBF]; relative cerebral blood volume [rCBV]; relative mean transit time [rMTT]; and relative time to peak [rTTP]). In addition to our main radiologic parameters of interest, we evaluated the following parameters that may be related to headaches. Significantly hypoperfused tissue volumes, infarct core volumes (rCBF < 30 ml/100 g/min), and “mismatch” (the difference between tissue volume in the hypoperfused area and infarct core) were recorded after processing by MISTar software. For collateral assessment, the regional leptomeningeal collateral score (rLMC) was used. Alberta stroke program early CT score (ASPECTS) and ASPECTS combined with posterior circulation ASPECTS (PC-ASPECTS) was calculated based on NCCT by two neuroradiologists, independently. The neuroradiologists were blinded to headache status during evaluation.

Data analyses

For descriptive purposes, the differences among continuous variables were analyzed by the Student's *t*-test or the Mann-Whitney *U* test, whereas the chi-square test assessed differences among categorical variables. Pearson's correlation coefficients were calculated to assess the relationship between the variables. Multiple adjusted logistic models were used to investigate the association between perfusion parameters and case status. Possible confounding factors were selected from the established variables and included in sequential models. First, we added demographic variables, including age and gender (model 1), and followed by the addition of clinical risk factors known to affect ischemic stroke, including TOAST classification, hyperlipidemia, diabetes, and hypertension (model 2). A subsequent model (model 3) adjusted for lifestyle, including smoking and alcohol consumption. A final model (model 4), extra adjusted for ASPECTS combined with

PC-ASPECTS and NIHSS at admission, which were measures of neurological function. Considering the collinearity between radiologic parameters of interest, we put them into different sequential models for analysis. In addition, non-diabetes patients and non-hyperlipidemic patients were used for sensitivity analysis to accurately assess the relationship between perfusion parameters and headache. The sample size was based on the available data. No statistical power calculation was conducted prior to the study. The level of significance was established at 0.05 for two-sided hypothesis testing. Statistical analysis was performed in SPSS 25.0 and GraphPad Prism 8.2.1.

RESULTS

Participants and their demographics and characteristics

A total of 190 patients with AIS were included in our study; 93 (48.9%) of them had concomitant headaches during the early phase of ischemic stroke, which was consistent with previous study results. Patient selection is illustrated in Figure 1. The average age of all patients was 64 (54.8, 73.0) years; 130 (68.4%) were men and the ratio of male to female was about 2:1; 141 (74.2%) patients had a hypertension history; 59 (31.1%) patients had a smoking history; NIHSS score (expressed as median and interquartile range [IQR]) at admission was 2 (0, 5.0) and NIHSS

score at discharge was 1 (0, 3.0); headache time relative to multimodal CT (expressed as median and IQR) was 6.0 (7.5, 11.0). Of these patients, 75.3% had large-artery atherosclerosis and 2.6% had an undetermined cause. Patient baseline characteristics are shown in Table 1.

Comparison of clinical and radiologic characteristics

Depending on whether the patient had a concomitant headache during the early phase of ischemic stroke or not, the participants were divided into two groups: the headache group with 93 patients and the non-headache group with 97 patients. Statistical analysis indicated significant differences in gender, hypertension, ASPECTS, rCBF, and rCBV between the two groups ($p < 0.05$). However, there were no significant differences in age, smoking, drinking, other medical histories except hypertension, stroke subtypes, NIHSS at admission and NIHSS score at discharge, headache time relative to multimodal CT, rLMC, ASPECTS combined with PC-ASPECTS, rTTP, rMTT, significantly hypoperfused tissue volume, or other factors between the two groups ($p > 0.05$; Table 1). The box plots in Figure 2 summarizes the data for rCBF, rCBV, rTTP, and rMTT results in the two groups.

Furthermore, we calculated the correlation coefficients among headache, TOAST classification, NIHSS at admission and discharge, ASPECTS, ASPECTS combined with

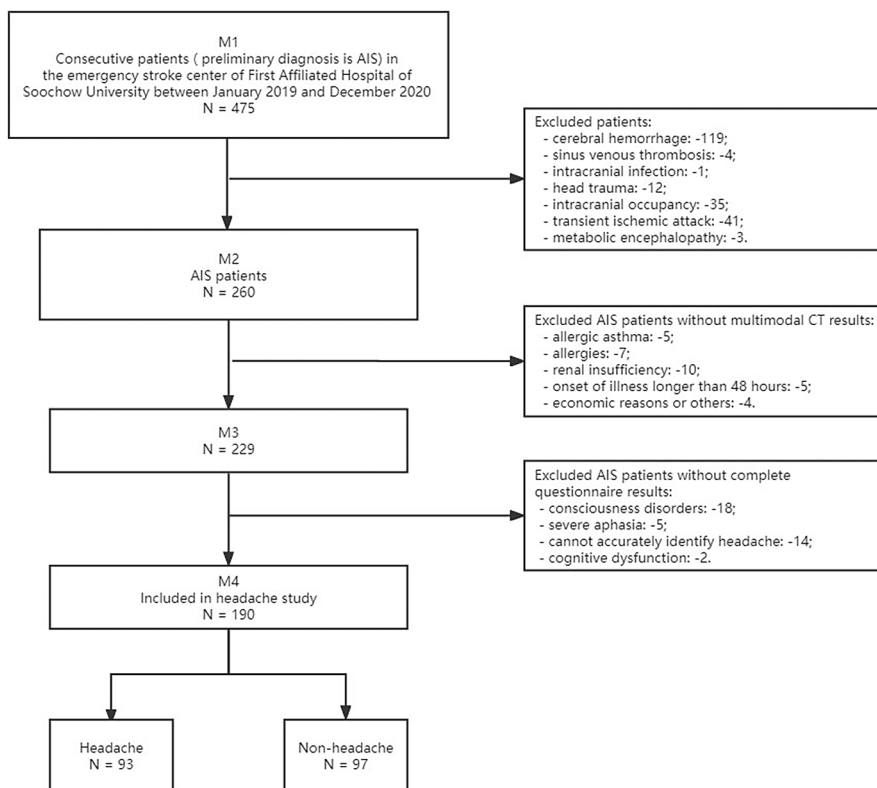


FIGURE 1 Flow diagram of participants' selection.

TABLE 1 Clinical and radiologic characteristics of patients with AIS

Characteristics	Total (n = 190)	Headache (n = 93)	Non-headache (n = 97)	p value
Age, median (IQR)	64.0 (54.8,73.0)	63 (52.0,72.0)	65 (56.0,74.0)	0.101
Male, n (%)	130 (68.4)	36 (38.7)	24 (24.7)	0.038
Hypertension, n (%)	141 (74.2)	62 (66.7)	79 (81.4)	0.02
Diabetes, n (%)	41 (21.6)	20 (21.5)	21 (21.6)	0.981
Hyperlipidemia, n (%)	36 (18.9)	15 (16.1)	21 (21.6)	0.332
Atrial fibrillation, n (%)	17 (8.9)	10 (10.8)	7 (7.2)	0.393
Coronary heart disease, n (%)	10 (5.3)	7 (7.5)	3 (3.1)	0.171
Smoking, n (%)	59 (31.1)	26 (28.0)	33 (34.0)	0.367
Alcohol consumption, n (%)	42 (22.1)	20 (21.5)	22 (22.7)	0.845
Stroke subtypes (based on TOAST classification)				
Large-artery atherosclerosis, n (%)	143 (75.3)	68 (73.1)	75 (77.3)	0.502
Small-vessel occlusion, n (%)	26 (13.7)	15 (16.1)	11 (11.3)	0.337
Cardioembolism, n (%)	12 (6.3)	4 (4.3)	8 (8.2)	0.264
Undetermined cause, n (%)	5 (2.6)	4 (4.3)	1 (1.0)	0.204
Specific cause, n (%)	4 (2.1)	2 (2.2)	2 (2.1)	1.000
NIHSS at admission, median (IQR)	2 (0, 5.0)	3 (0, 6)	2 (0.5, 5)	0.413
NIHSS at discharge, median (IQR)	1 (0, 3.0)	1 (0, 4)	1 (0, 2.5)	0.700
Barthel index at admission, median (IQR)	72.5 (30.0, 95.0)	70 (35, 95)	75 (30, 95)	0.752
Barthel index at discharge, median (IQR)	87.5 (55.0, 100.0)	85 (55, 100)	90 (50, 100)	0.871
ASPECTS, median (IQR)	10 (9.0, 10.0)	10 (9.0, 10.0)	9 (9.0, 10.0)	0.006
ASPECTS combined with PC-ASPECTS, median (IQR)	19 (18.0, 20.0)	19 (18.0, 20.0)	19 (18.0, 20.0)	0.275
Headache time relative to multimodal CT, median (IQR)	6.0 (7.5, 11.0)	8.0 (6.0, 11.0)	7.0 (5.5, 12.0)	0.768
rCBF, median (IQR)	0.75 (0.50, 0.92)	0.70 (0.48, 0.84)	0.81 (0.54, 0.98)	0.024
rCBV, median (IQR)	0.89 (0.70, 1.09)	0.82 (0.64, 1.03)	0.96 (0.80, 1.13)	0.001
rTTP, median (IQR)	1.07 (1.01, 1.26)	1.12 (1.02, 1.29)	1.05 (1.00, 1.20)	0.055
rMTT, median (IQR)	1.21 (1.03, 1.87)	1.30 (1.05, 1.91)	1.16 (1.02, 1.74)	0.301
Significantly hypoperfused tissue volume, median (IQR)	0 (0, 34.5)	5.00 (0, 36.00)	0 (0, 34.75)	0.388
Infarct core, median (IQR)	0 (0, 3.0)	0 (0, 4.00)	0 (0, 2.00)	0.264
Mismatch, median (IQR)	0 (0, 34.0)	3 (0, 34.50)	0 (0, 33.50)	0.478

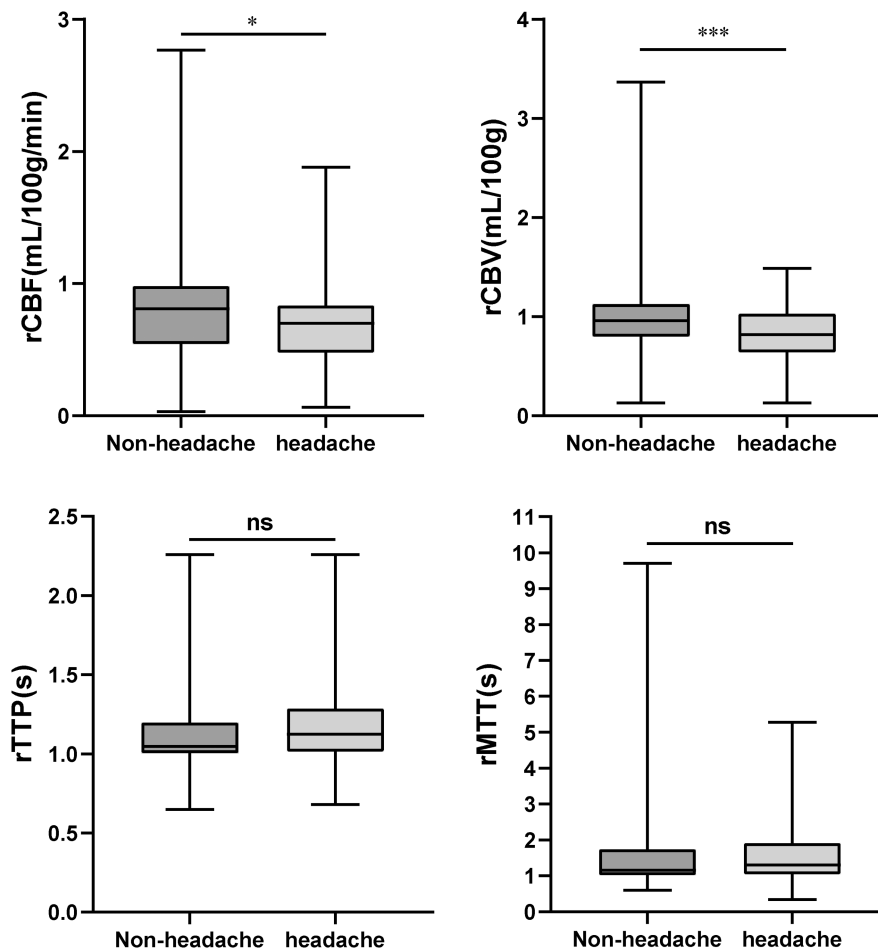
Abbreviations: AIS, acute ischemic stroke; ASPECTS, Alberta Stroke Program Early CT Score; CT, computed tomography; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; PC-ASPECTS, posterior circulation ASPECTS; rCBF, relative cerebral blood flow; rCBV, relative cerebral blood volume; rMTT, relative mean transit time; rTTP, relative time to peak; TOAST, Trial Org 10172 in Acute Stroke Treatment.

PC-ASPECTS, rCBF, rCBV, rTTP, and rMTT, and observed correlation coefficients: $r = 0.201$ between the headache and ASPECTS ($p < 0.001$); $r = -0.164$ between the headache and rCBF ($p < 0.05$); and $r = -0.253$ between the headache and rCBV ($p < 0.001$). Concomitant headache during the early phase of ischemic stroke had weak but significant correlations with ASPECTS, rCBF, and rCBV (Table 2).

CBF and CBV were associated with concomitant headache

Multiple adjusted logistic models were used to determine radiologic parameters that were significantly associated with concomitant headache during the early phase of ischemic stroke. The forest plot in Figure 3 summarizes these data.

FIGURE 2 Box plots for rCBF, rCBV, rTTP, and rMTT results in two groups. rCBF, relative cerebral blood flow; rCBV, relative cerebral blood volume; rMTT, relative mean transit time; rTTP, relative time to peak.



In the demographic-adjusted model (model 1), only rCBV was significantly associated with concomitant headache (adjusted odds ratio [OR], 0.181. 95% confidence interval [CI], 0.065–0.504, $p < 0.001$). These associations were robust after adjusting for sociodemographic characteristics and other confounding factors (model 4: adjusted OR, 0.160; 95% CI, 0.055–0.461, $p < 0.001$).

However, we could distinguish a potential trend about rCBF in sequential models. The p values for the ORs were marginally significant in primary models and were intensified in adjusted models. Significant association was detected for rCBF (adjusted OR, 0.309, 95% CI, 0.113–0.844, $p < 0.05$) after adjusting for demographics, cardiovascular risk factors, lifestyle choices, medical histories, and stroke severity (Figure 3).

Compared with rCBF, rTTP, and rMTT also showed similar trends that these ORs were marginally significant in the demographic-adjusted model and were intensified in the fully adjusted model. Nevertheless, there were no significant associations among rTTP, rMTT, and risk of concomitant headache in the overall sample (Figure 3). Full results of models with covariates are shown in Tables S1–S4.

Sensitivity analysis

The effect estimates were similar to those of the main models when we used related radiologic parameters of non-diabetes patients and non-hyperlipidemic patients to analyze its association with concomitant headache. When we performed multiple adjusted logistic models, the direction and significance of our results were consistent. We could distinguish a similar potential trend about CBF and CBV in sequential models (Tables S5 and S6). CBF was significantly associated with concomitant headache in non-diabetes patients, whereas CBV was significantly associated with concomitant headache in non-diabetes patients and non-hyperlipidemic patients (Tables S5 and S6). In general, our analyses provided evidence of robustness in our results.

DISCUSSION

In our study, the concomitant headache during the early phase of ischemic stroke was analyzed with related radiologic parameters as well as clinical data. The main results showed a close correlation between regional

TABLE 2 Pearson correlation coefficients between the variables

	Headache	TOAST classification	NIHSS at admission	NIHSS at discharge	ASPECTS	ASPECTS combined with PC-ASPECTS	rCBF	rCBV	rTTP	rMTT
Headache	1	0.045	0.059	0.028	0.201**	0.079	-0.164*	-0.253**	0.141	0.075
TOAST classification	0.045	1	-0.004	-0.012	-0.003	-0.018	0.027	-0.053	0.005	-0.009
NIHSS at admission	0.059	-0.004	1	0.845**	-0.204**	-0.148*	-0.302**	-0.077	0.279**	0.371**
NIHSS at discharge	0.028	-0.012	0.845**	1	-0.247**	-0.219**	-0.343**	-0.057	0.294**	0.406**
ASPECTS	0.201**	-0.003	-0.204**	-0.247**	1	0.761**	0.199**	-0.005	-0.274**	-0.223**
ASPECTS combined with PC-ASPECTS	0.079	-0.018	-0.148*	-0.219**	0.761**	1	0.157*	0.049	-0.217**	-0.153*
rCBF	-0.164*	0.027	-0.302**	-0.343**	0.199**	0.157*	1	0.562**	-0.614**	-0.707**
rCBV	-0.253**	-0.053	-0.077	-0.057	-0.005	0.049	0.562**	1	-0.175*	-0.079
rTTP	0.141	0.005	0.279**	0.294**	-0.274**	-0.217**	-0.614**	-0.175*	1	0.685**
rMTT	0.075	-0.009	0.371**	0.406**	-0.223**	-0.153*	-0.707**	-0.079	0.685**	1

Note: * $p < 0.05$; ** $p < 0.01$.

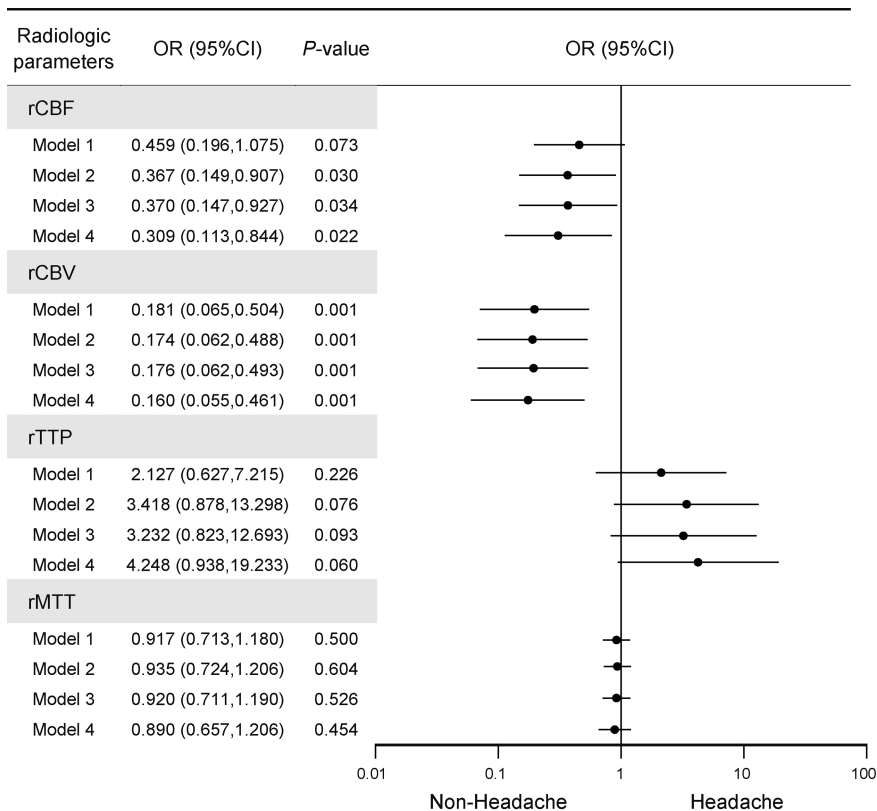
Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; NIHSS, National Institutes of Health Stroke Scale; PC-ASPECTS, posterior circulation ASPECTS; rCBF, relative cerebral blood flow; rCBV, relative cerebral blood volume; rMTT, relative mean transit time; rTTP, relative time to peak; TOAST, Trial Org 10172 in Acute Stroke Treatment.

hypoperfusion and concomitant headache. It revealed that, in addition to collateral circulation, microcirculation might play an important role in this separate clinical entity.

Although the pathogenesis of concomitant headache during stroke is still unclear, some reasonable hypotheses have been put forward, including centrally driven lesion patterns, the necessary role of vessel wall elasticity, and susceptibility to SDs.^{7,11,12} Mechanisms producing pain in ischemic stroke must be different compared to other peripheral artery diseases due to the absence of pain receptors in brain tissue.^{13,14} Studies showed lesions in the somatosensory cortex seem to predispose for headache in stroke.^{11,15} These provided pieces of evidence for the notion that headache in stroke might be centrally driven. Ischemic stroke is a disorder of blood flow to the brain. Concurrently, profound changes in cerebral blood flow were associated with SDs.^{12,16} Cortical hyperexcitability involves disturbance of Na/K-ATPase activity and decreased efflux of cations, which may be associated with hypoperfusion disorders.^{16,17} Multimodal CT expands the role of emergency imaging examination by providing physiologic insights into cerebral hemodynamics and determining the consequences of vessel occlusions and stenoses.^{18,19} We were especially interested in relevant radiologic parameters that could reflect these characteristics. Our data suggested that blood perfusion in the lesion area might be an important factor. Hypoperfusion possibly facilitating the activation of perivascular nerve fibers leading to headache.

Vascular elasticity is closely related to vasodilation of large vessels (clot extent), collateral circulation, and microcirculation.²⁰⁻²² In previous studies, the concept of the neurovascular unit as the key brain component affected by stroke was proposed.²³⁻²⁵ Current definitions of this entity include endothelial cells, neurons, and glia within millimeters of cerebral capillary microcirculation.^{26,27} CTP and CTA could provide a further assessment of the microcirculation, and reflect the local cerebral perfusion pressure, which is a primary factor controlling the cerebral circulation.^{28,29} CTP tracks the bolus of contrast over time to generate time-density curves for each voxel.⁹ Then, based on the central volume principle, perfusion parameters could be derived from the tissue-time density curve.^{9,28} CBV is proportional to the area under the curve, whereas CBF is proportional to the amplitude of the curve.^{9,28} MTT maps can also be calculated as the CBV/CBF after correction.^{9,28} Among these parameters, the CBV lesion reflects the infarct core, and the CBF or MTT lesion reflects the surrounding region of hypoperfused “penumbral” tissue.^{30,31} Although headaches seem to be more frequent in patients with larger infarct cores, recent studies suggested that clot extent and infarct volumes were not related to

FIGURE 3 Adjusted odds ratio with 95% confidence intervals for radiologic parameters and concomitant headache associated with ischemic stroke.



Abbreviations: OR, odds ratio; CI, confidence intervals.

Model 1 adjusted for age and gender.

Model 2 adjusted for model 1 covariates + TOAST classification, hyperlipidemia, diabetes, and hypertension.

Model 3 adjusted for model 2 covariates + smoking and alcohol consumption.

Model 4 adjusted for model 3 covariates + ASPECTS combined with PC-ASPECTS and NIHSS at admission.

headaches.^{7,11} Meanwhile, our findings suggested the difference in collateral circulation between the two groups was not statistically significant. Therefore, besides control perfusion arteries and collateral circulation, the microcirculation may play an important role in this pathophysiological process.

Our data should be interpreted with some caution due to the limitations of the study. This was an exploratory analysis, not powered, and did not account for multiple comparisons. Because the participants in this study were recruited only from one clinical unit and the study relied on participants' answers for headache questionnaires, which might have affected the generalizability of the results (the proportion of severe stroke and cardioembolic stroke is relatively low), there may have been bias inherent. However, the influence of this possible source of selection bias is likely to be small due to the small size of the sample. In order to reduce the impact of small sample size and confounding on statistical correlation, we use multiple adjusted logistic models and sensitivity analysis to enhance statistical efficiency. Meanwhile, in order to address the questions about exclusion bias, we analyzed the data on the characteristics of excluded subjects and compared them with the

data of the final sample (Table S7). There were no significant differences among the three groups ($N = 260$, $N = 229$, and $N = 190$). In general, our analyses provided evidence of robustness in our results. In addition, considering CTP is software-dependent in general, quantification bears uncertainty. Penumbra and infarct core volume could only be assessed in the anterior circulation because of the lack of validated thresholds for the posterior circulation.

CONCLUSION

In summary, patients with lower rCBF and rCBV tended to experience the concomitant headache during the early phase of ischemic stroke. Controls of regional hypoperfusion should be considered a potential target for future therapeutic intervention of the concomitant headache.

AUTHOR CONTRIBUTIONS

Y.G., Y.Y., and J.N. wrote the manuscript. Y.G., Y.Y., and J.N. designed the research. Y.G., W.D., H.L., X.Z., and S.H. performed the research. Y.G. and Y.Y. analyzed the data.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

DATA AVAILABILITY STATEMENT

Original data of the present study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study involving human participants was reviewed and approved by the Institutional Review Board of The First Affiliated Hospital of Soochow University. The procedures used in this study adhere to the tenets of the Declaration of Helsinki. The experiments comply with the current laws of the country in which they were performed. All patients gave written informed consent.

ORCID

Yi Yang  <https://orcid.org/0000-0001-7896-9485>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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