Article

J. Biol. Regul. Homeost. Agents. 2022; 36(5): 1535–1541
https://doi.org/10.23812/j.biol.regul.homeost.agents.20223605.163

Correlation of Plasma Asymmetric Dimethylarginine Expression with Early Neurological Deterioration and Recurrence in Patients with Acute Cerebral Infarction

Yuanwei Wang[1,2,*], Li Du[1], Xian Zhang[1], Ying Wang[1], Liwu Lu[1], Rui Wei[1], Benchi Xu[1], Xiaojie Hu[1]

[1]Department of Neurology, The Affiliated Shuyang Hospital of Xuzhou Medical University, Shuyang Hospital, 223600 Shuyang, Jiangsu, China
[2]Department of Rehabilitation, The Affiliated Shuyang Hospital of Xuzhou Medical University, Shuyang Hospital, 223600 Shuyang, Jiangsu, China
*Correspondence: wyw170285@163.com (Yuanwei Wang)
Published: 20 October 2022

Background: This study investigated the correlation between the expression of asymmetric dimethylarginine (ADMA) in plasma and early neurological deterioration (END) as well as early recurrence of acute cerebral infarction (ACI).
Methods: A total of 160 ACI cases were divided into the following five groups based on the occurrence of END and early recurrence: Group A (n = 48, had END at first admission), group B (n = 112, without END at first admission), group C (n = 32, with early recurrence 3 months after discharge), group D (n = 128, without early recurrence 3 months after discharge), group E (n = 17, patients in group A with early recurrence 3 months after discharge). Fifty healthy people during the same period were selected as controls. Participants' blood glucose, blood pressure, hemoglobin and urine protein were measured biochemically, and ADMA levels in their plasma were measured by ELISA (enzyme linked immunosorbent assay). Further, the correlation of ADMA expression in the plasma of ACI patients with biochemical parameters, NIHSS (national institutes of health stroke scale) score, early recurrence and cerebral infarction area was performed using the Pearson's method.
Results: The results showed that compared with healthy people, the expression of ADMA was significantly higher in the blood of ACI patients and even higher in ACI patients with END. Logistic regression analysis indicated that ADMA level was a risk factor for END and early recurrence in ACI patients. Besides, ADMA levels were positively correlated with NIHSS score, early recurrence of ACI and cerebral infarction.
Conclusions: These findings indicated ADMA as a potential diagnostic marker for END and early recurrence of ACI.

Keywords: acute cerebral infarction; early neurological deterioration; early recurrence; ADMA

Introduction

As one of the leading causes of death worldwide [1], stroke can be divided into ischemic and hemorrhagic. Ischemic stroke can lead to acute cerebral infarction (ACI) if local blood flow is not recovered in a short time [2]. ACI is a series of neurological dysfunction symptoms arising due to ischemia and hypoxia of local brain tissue. ACI accounts for 87% of all strokes, and notably, the incidence of cerebral infarction among young people is increasing due to stress and unhealthy lifestyles [3]. The incidence of cerebral infarction in the Chinese population ranks among the highest in the world, and cerebrovascular disease has become the leading cause of death in China [4]. Approximately 10% of patients with mild stroke suffer from recurrence within the first week.

Early neurological deterioration (END) is a common event in acute stroke [5], with an incidence of 20% to 40% and associated with the deterioration of clinical outcomes [6]. Recurrent infarction is also a potential contributor to neurological deterioration after stroke. Previous findings showed that ACI could lead to severe sequelae such as disability or even death unless timely treated [7]. These findings highlight the importance of early diagnosis of ACI to improve treatment outcomes and reduce the potential risk of sequelae and death. Currently, the diagnosis of ACI relies mainly on traditional neuroimaging methods, which include computed tomography (CT) and magnetic resonance imaging (MRI). Although imaging techniques are significant in ruling out hemorrhagic stroke, CT fails to display ischemic foci clearly in the early stage of infarction. At the same time, MRI is problematic for patients with metal stents [8]. Given such limitations, the examination of circulating biomarkers is now being applied for diagnosing diseases or assessing clinical findings, which is rapid and inexpensive. Though the diagnostic value of C-reactive protein (CRP) and interleukin-6 for ACI has been considered, their clinical use is relatively limited due to their low specificity [9]. Therefore, identifying sensitive biomarkers is vital for the accurate diagnosis and prognostic assessment of ACI.

Copyright: © 2022 The Author(s). Published by Biolife Sas. This is an open access article under the CC BY 4.0 license.
Note: *J. Biol. Regul. Homeost. Agents.* stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

Asymmetric dimethylarginine (ADMA) is a naturally occurring toxic amino acid. It is an analog of L-arginine and can act as an endogenous competitive inhibitor of nitric oxide (NO) synthase [10]. In healthy individuals, the enzyme dimethylarginine dimethylaminohydrolase (DDAH) converts the toxic ADMA to l-citrulline and dimethylamine [11]. DDAH is expressed in many tissues and cells, including the kidney, pancreas, brain, liver, lung, endothelial cells, and cardiomyocytes. According to previous studies, accumulation of ADMA could result in impaired endothelial function of forearm resistance arteries, increased systemic vascular resistance and arterial blood pressure, and decreased cardiac output. At first, ADMA in urine was only proved to be associated with uremia but later confirmed that ADMA is a toxic non-protein amino acid in human diseases [12]. Recent clinical and experimental evidence has suggested that ADMA is also involved in pathophysiological disorders of vascular endothelial function, atherosclerosis, inflammation, apoptosis, and impaired immune function [13]; The predictive values of ADMA for cardiovascular events have also been reported.

Increased plasma ADMA concentration is directly related to coronary artery disease, occlusive peripheral arterial disease, and diabetes [14]. Zhang *et al.* [15] have reported that ADMA and homocysteine (Hcy) are the causative factors for the development of ACI in the Chinese population, and plasma concentrations of ADMA and Hcy were positively correlated with other risk factors (age, systolic pressure, diastolic pressure, and total cholesterol). Thus, ADMA may be associated with the occurrence of ACI. However, so far, the specific link between them remains unknown.

In this study, we intended to elucidate the relationship between ADMA and ACI through clinical trials to provide experimental data for finding predictors of END and early recurrence of ACI and targets for intervention therapy.

Materials and Methods

Study Subjects

The patients were divided into two groups based on with or without END (referring to an increase of National Institute of Health (NIH) Stroke Scale score ≥2 within three days at first admission, named as event a): Group A (n = 48, with event a), group B (n = 112, without event a). Also, patients were divided into two groups based on with or without early recurrence (occurring three months after discharge, named event b): Group C (n = 32, with event b), group D (n = 128, without event b). Additionally, patients in group A who also had event b were categorized as group E (n = 17). Fifty healthy people who underwent physical examinations during the same period were recruited as the control group. All patients were followed up for six months after the initial treatment, and the incidence of adverse events/complications, including postoperative recurrence and death, was recorded during follow-up. The study protocol was performed following the Declaration of Helsinki. The screening process of patients is shown in Fig. 1.

We assessed the data of 160 patients diagnosed with ACI in our hospital from March 2019 to September 2020. The inclusion criteria of the study were: (1) ACI confirmed by imaging (brain CT), (2) aged 18 to 80 years old, (3) visited the hospital within 24 h of onset, and (4) who provided signed informed consent to participate. The exclusion criteria include: (1) Simultaneously diagnosed with other malignant tumors or organ dysfunction in addition to ACI, (2) the presence of severe systemic infection in addition to ACI, (3) developed hemorrhagic transformation, (4) who underwent thrombolytic therapy (arterial and venous), and (5) who had a mental illness, severe cognitive impairment or language problems.

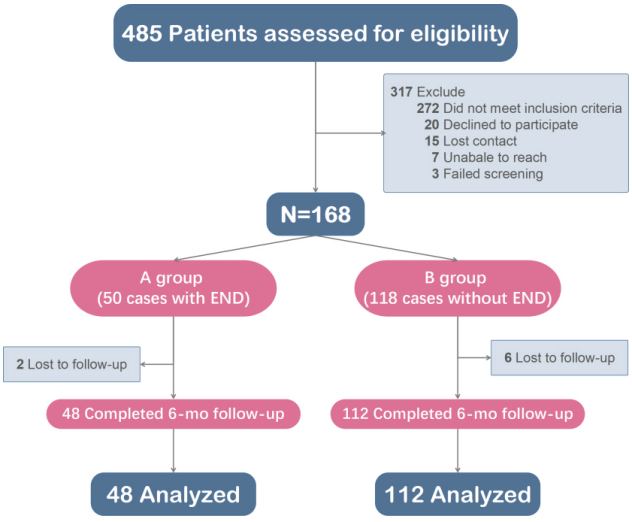

Fig. 1. Flow chart of patients screening.

Blood Pressure Measurement

All patients' blood pressure was measured before and after treatment using a Yuwell sphygmomanometer (PBA007002P). The frequency of blood pressure recordings was as follows: First 15 min/time for 1 h, then 30 min/time for 6 h, and finally 1 h/time until 72 h.

Biochemical Indicators Detection

Fasting (12 h) blood samples (3 mL) were collected from the cubital vein of each patient. The blood samples were collected in lithium heparin anticoagulant tubes, followed by centrifugation at 3000 r/min for 10 min. The plasma collected was used to measure blood glucose, hemoglobin, urine protein, fibrinogen, CRP, triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) using an automatic biochemical analyzer. Plasma ADMA concentrations

Table 1. Clinical characteristics of ACI patients and the healthy controls.

Variables	ACI patients (n = 160)	Healthy controls (n = 50)	p value
Age	62.88 ± 11.63	61.56 ± 10.32	0.473
Gender (male/female)	88/72	26/24	0.710
BMI	23.81 ± 3.17	23.39 ± 2.78	0.400
Signs and symptoms, n (%)			
Headache	76 (47.5)		
Dizziness	74 (46.3)		
Hemidysesthesia	65 (40.6)		
Quadriplegia, dysarthria	33 (20.6)		
Disturbance of consciousness	15 (9.4)		
Area of cerebral infarction (cm)	2.49 ± 1.58		
Onset time	≤24 h		
NIHSS when admitted (score)	6.00 ± 1.98		
Smoking, n (%)	78 (48.8)	16 (32.0)	0.038
Alcoholics, n (%)	66 (41.3)	12 (24.0)	0.028
History of hypertension, n (%)	90 (56.3)	14 (28.0)	0.000
History of diabetes, n (%)	82 (51.3)	15 (30.0)	0.009
History of coronary heart disease, n (%)	46 (28.8)	10 (20.0)	0.222
History of hyperlipidemia, n (%)	63 (39.4)	13 (26.0)	0.086
Creatinine (μmol/L)	89.18 ± 11.95	90.40 ± 11.72	0.528
ALT (U/L)	21.89 ± 8.20	23.03 ± 7.07	0.380
TG (mmol/L)	1.53 ± 0.54	1.35 ± 0.47	0.029
LDL (mmol/L)	3.78 ± 0.87	3.00 ± 0.78	0.020
HDL (mmol/L)	1.00 ± 0.34	1.23 ± 0.39	0.000
HbA1c (%)	5.97 ± 1.49	5.28 ± 1.69	0.006
Folic acid (μg/L)	11.77 ± 3.16	13.82 ± 6.22	0.029
CRP (mg/L)	2.72 ± 0.81	2.16 ± 0.72	0.000
Hcy (μmol/L)	15.51 ± 3.67	11.91 ± 3.59	0.000
ADMA (μmol/L)	0.91 ± 0.31	0.32 ± 0.09	0.000

BMI, body mass index; ALT, alanine aminotransaminase; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, glycosylated hemoglobin; CRP, C-reactive protein; Hcy, homocysteine; ADMA, asymmetric dimethylarginine.

were determined with commercially available enzyme-linked immunosorbent assay kits (Elabscience Biotechnology Co., Ltd., E-EL-0042c, Wuhan, China).

Statistical Analysis

We used SPSS 24.0 software (IBM SPSS statistics, Chicago, IL, USA) for data analysis. The data are expressed as mean ± standard deviation (SD), and a t-test was used to compare between two groups. Enumeration data are expressed as frequency (n) and rate (%), which were analyzed by χ^2 test. Multivariate logistic regression analysis was used to predict the influencing factors of ACI, and Pearson's test was used to analyze the correlation between ADMA levels and different factors. $p < 0.05$ was considered statistically significant.

Results

Baseline Characteristics of the Study Participants

There were no significant differences in age, gender, and body mass index between the ACI patients and healthy controls. ACI patients mostly had symptoms such as headache (47.5%), dizziness (46.3%), and hemidysesthesia (40.6%). The onset time of all patients was ≤24 h each time. The NIH Stroke Scale (NIHSS) score on admission was 6.00 ± 1.98. Compared with the controls, the ACI group had more patients with a smoking and drinking history and a history of hypertension and diabetes. Regarding blood parameters, TG, LDL, glycosylated hemoglobin, CRP, Hcy, and ADMA were significantly up-regulated, while folic acid and HDL were significantly down-regulated in ACI patients (Table 1).

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

Table 2. Comparison of follow-up after treatment between groups A and B.

Variables	Group A (n = 48 [%])	Group B (n = 112 [%])	p value
Recurrence rate after treatment			
1st month	8 (16.7)	4 (3.6)	0.000
3rd month	16 (33.3)	8 (7.1)	0.000
6th month	20 (41.7)	12 (10.7)	0.000
Complications			
Death	3 (6.3)	2 (1.8)	
Cerebral hemorrhage	5 (10.4)	3 (2.7)	
Vascular stenosis	4 (8.3)	3 (2.7)	
Pulmonary stenosis	8 (16.7)	8 (7.1)	
Lower extremity deep venous thrombosis	6 (12.5)	10 (8.9)	
Total	13 (27.1)	15 (13.4)	0.037

Table 3. Multivariate logistics regression analysis of early neurological deterioration in ACI patients.

Risk factors	Odds ratio	95% confidence interval	p value
Age	1.10	0.52–1.95	0.392
Gender	1.03		0.084
Cerebral infarction area	2.12	1.35–5.14	0.002
NIHSS	1.93	1.23–4.59	0.000
History of smoking	1.19	0.63–2.96	0.192
Alcoholics	1.23	0.92–2.93	0.074
History of hypertension	2.01	0.83–4.23	0.223
History of diabetes	1.18	0.86–1.70	0.063
History of coronary heart disease	1.48	0.85–3.95	0.088
History of hyperlipidemia	1.22	0.79–2.23	0.493
Creatinine	1.16	0.87–2.29	0.092
TG	1.32	0.95–3.02	0.335
LDL	1.29	0.93–2.55	0.293
HDL	0.83	0.58–2.34	0.834
HbA1c	1.24	1.08–3.94	0.025
Folic acid	0.94	0.65–1.23	0.079
CRP	1.37	1.02–2.32	0.015
Hcy	2.31	1.18–7.52	0.000
ADMA	2.45	1.16–6.94	0.000

Comparison of Recurrence Rate and Complications during Follow-Up between Different Groups

We have compared the recurrence rate and complications between different groups in the 1st, 3rd, and 6th months after treatment. The results showed that the recurrence rates in the 1st (16.7%), 3rd (33.3%), and 6th months (41.7%) in group A were significantly higher compared to group B. When compared to group B (13.4%), thirteen patients in group A (27.1%) had complications, which include three deaths (6.3%), five cerebral hemorrhages (10.4%), four vascular stenoses (8.3%), eight pulmonary infections (16.7%) and six lower extremity deep venous thrombosis (12.5%) (Table 2). These findings indicated that ACI patients with END had a higher recurrence rate and poorer prognosis.

Logistic Regression Analysis of the Influencing Factors of Early Neurological Deterioration and Recurrence in Patients with Acute Cerebral Infarction

Multivariate logistic regression was performed to analyze factors influencing the onset of END and early recurrence of ACI. Cerebral infarction area (OR (odds ratio) = 2.12, 95% Cl (confidence interval): 1.35–5.14), NIHSS score (OR = 1.93, 95% Cl: 1.23–4.59), glycosylated hemoglobin (OR = 1.24, 95% Cl: 1.08–3.94), CRP (OR = 1.37, 95% Cl: 1.02–2.32), Hcy (OR = 2.31, 95% Cl: 1.18–7.52) and ADMA expression (OR = 2.45, 95% Cl: 1.16–6.94) were found to be risk factors affecting END in patients with ACI (Table 3). Age (OR = 1.35, 95% Cl: 1.05–2.94), cerebral infarction area (OR = 2.33, 95% Cl: 1.09–3.88), NIHSS score (OR = 2.26, 95% Cl: 1.13–4.95), history of hypertension (OR = 1.65, 95% Cl: 1.12–4.93), history of diabetes (OR = 1.49, 95% Cl: 1.09–3.80), his-

Table 4. Multivariate logistics regression analysis of early recurrence in ACI patients.

Risk factors	Odds ratio	95% confidence interval	*p* value
Age	1.35	1.05–2.94	0.023
Gender	1.02	0.93–2.38	0.452
Cerebral infarction area	2.33	1.09–3.88	0.000
NIHSS	2.26	1.13–4.95	0.000
History of smoking	1.23	0.87–2.85	0.193
Alcoholics	1.30	0.95–2.03	0.075
History of hypertension	1.65	1.12–4.93	0.032
History of diabetes	1.49	1.09–3.80	0.024
History of coronary heart disease	1.23	0.96–1.93	0.390
History of hyperlipidemia	1.83	1.03–2.74	0.042
Creatinine	1.02	0.88–3.24	0.653
TG	1.35	0.89–2.09	0.294
LDL	1.65	1.02–3.96	0.049
HDL	0.79	0.43–0.92	0.018
HbA1c	1.44	0.95–3.05	0.083
Folic acid	1.22	0.92–2.80	0.057
CRP	1.35	0.98–2.93	0.084
Hcy	2.60	1.19–5.93	0.000
ADMA	2.25	1.24–6.39	0.000

tory of hyperlipidemia (OR = 1.83, 95% Cl: 1.09–3.80), LDL (OR = 1.65, 95% Cl: 1.02–3.96), HDL (OR = 0.79, 95% Cl: 0.43–0.92), Hcy (OR = 2.60, 95% Cl: 1.19–5.93) and ADMA expression (OR = 2.25, 95% Cl: 1.24–6.39) were found to be the risk factors for early recurrence in ACI patients (Table 4). These results suggested that plasma ADMA level, cerebral infarction area, NIHSS score, and some biochemical parameters (HbA1c, CRP and Hcy) related to cerebral infarction have an important role in indicating END and early recurrence in patients with ACI.

Comparison of Plasma ADMA Levels

We examined the levels of ADMA in different groups of patients. At first admission, the expression level of plasma ADMA between groups A and B was significantly higher compared to the healthy control group. The expression level in group A was higher than in group B. Three months after discharge, the expression level of ADMA in groups C and D was increased compared to the control group. The expression level in group C was even higher. The expression level of ADMA in group E was significantly increased compared to the control group (Table 5). Overall, ACI patients with END or early recurrence were associated with higher levels of plasma ADMA. In comparison, those who suffered from both END and early relapse had higher levels of ADMA.

Correlation between Plasma ADMA Expression and the Parameters Related to Cerebral Infarction in Patients with Acute Cerebral Infarction

Pearson's method was employed to analyze the correlation between plasma ADMA expression and biochemical parameters, NIHSS score, early recurrence, and cerebral infarction area in patients with ACI. The results indicated that ADMA expression was positively correlated with NIHSS score, cerebral infarction area, and early recurrence. Also, ADMA level was positively correlated with HbA1c, TG, LDL, CRP, and Hcy levels but negatively correlated with folic acid and HDL levels (Table 6).

Table 5. Comparison of plasma ADMA levels in different groups of patients.

Group	n	ADMA (μmol/L)
A	48	$1.12 \pm 0.33^{***\#\#\#}$
B	112	$0.82 \pm 0.25^{***}$
C	32	$1.10 \pm 0.26^{***\&\&\&}$
D	128	$0.86 \pm 0.30^{***}$
E	17	$1.24 \pm 0.20^{***}$
Control group	50	0.32 ± 0.09

Note: $^{***}p < 0.001$ vs. Control group; $^{\#\#\#}p < 0.001$ vs. Group B; $^{\&\&\&}p < 0.001$ vs. Group D.

Discussion

Cardiovascular and cerebrovascular diseases have become the prevailing health problems and are affecting an increasing number of people. Cerebral infarction has a high rate of recurrence, disability, and mortality. END, indicating a poor prognosis, attacks about one-third of patients diagnosed with ACI within 3 to 7 days after admission [16]. The disability/mortality rate of patients with cerebral infarction is 34.5 to 37.1% after three months and 33.4 to 44.6% after one year of onset [17] . The annual and within five years recurrence rate is as high as 17.7% and 40%, respec-

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

Table 6. Correlation between plasma ADMA expression and parameters related to cerebral infarction.

Variables	ADMA, *r*	*p* value
NIHSS score	0.662	0.000
Cerebral infarction area	0.692	0.000
Early recurrence	0.323	0.000
Creatinine	0.137	0.085
HbA1c	0.283	0.000
ALT	0.097	0.224
TG	0.391	0.000
LDL	0.638	0.000
HDL	–0.446	0.000
CRP	0.441	0.000
Hcy	0.483	0.000
Folic acid	–0.351	0.000

tively, after treatment [18]. Although there are many treatments for cerebral infarction, they often have little effect and are costly. Suppose there is a feasible predictive and therapy approach to END and recurrence of cerebral infarction. In that case, the mortality rate and poor prognosis are bound to be improved with early prevention and treatment. After 6-month follow-up in ACI patients, we found that ACI patients with END were more vulnerable to recurrence and complication than those without END, indicating a poor prognosis consistent with previous studies.

C-reactive protein (CRP) is an acute-phase protein synthesized by hepatocytes when the body is stimulated by inflammatory insults, including microbial invasion or tissue injury [19]. CRP removes necrotic and apoptotic cells and pathogens by activating the complement and mononuclear phagocytic systems upon binding to its ligands. As many as three-quarters of patients with ACI have elevated CRP in serum, suggesting that CRP can be used as a potential prognostic biomarker for ACI [20]. In our study, CRP levels were also significantly increased in ACI patients, recognized as a risk factor for developing END and early recurrence in ACI patients. Logistics regression analysis showed that factors affecting END and early recurrence in ACI patients encompassed smoking history, alcoholism, ADMA expression, NIHSS score, and cerebral infarction area, which has also been proven by some other studies [21].

Interestingly, this study found that ADMA levels in plasma constitute a risk factor for END and early recurrence in ACI patients. Plasma ADMA expression was significantly increased in patients with ACI compared to healthy people, and its expression in patients with END was higher than those without END. ADMA is an endogenous inhibitor of nitric oxide synthase (NOS). It binds nitric oxide synthase competitively and inhibits its activity, thus reducing nitric oxide production and triggering inflammatory responses and endothelial dysfunction [22]. Studies have confirmed that ADMA was associated with carotid intima-media thickness [23–25]. Wanby *et al*. [26] found that ADMA levels in the blood of the Swedish population can be used as a risk marker for the development of stroke and acute cerebrovascular disease. Scherbakov *et al*. [27] discovered that ADMA levels in the blood could be used not only as a diagnostic marker for stroke but also as a predictive target for peripheral vascular endothelial dysfunction.

In this study, for the first time, we found that ADMA levels were significantly higher in ACI patients three months after discharge than in healthy people. Among these patients, its expression was significantly higher in ACI patients who developed early recurrence than those who did not and higher in patients with END and early recurrence than healthy controls. Therefore, ADMA demonstrated potential as a diagnostic marker in patients with ACI. In addition, we found that ADMA levels in plasma were positively correlated with creatinine, glycosylated hemoglobin, TG, LDL, CRP, and serum Hcy levels and negatively correlated with folic acid and HDL levels. These observations coincided with the findings of Kołakowska *et al*. [28], who reported a positive correlation between ADMA level and the mean high-sensitivity CRP in hypertensive patients. ADMA levels were also positively correlated with NIHSS score, early recurrence of ACI, and cerebral infarction area, implying that the expression level of ADMA in plasma might predict END and early recurrence in ACI.

Conclusions

The results of this study indicate that increased plasma ADMA levels were a risk factor for END and early recurrence in patients with ACI and were positively correlated with END and early recurrence in patients with ACI. These findings suggest that ADMA might be a good predictor of END and early cerebral infarction recurrence and a possible intervention therapy target. However, this study has some limitations in its coverage, and a larger sample size is certainly warranted for further validation in the future.

Author Contributions

YWW and RW—designed the study; LD and LWL—drafted the article; XZ and BCX—collected data; YW and XJH—managed and analyzed the data. All authors interpreted the data and approved the final version of the article.

Ethics Approval and Consent to Participate

Informed consent was obtained from all patients, and this study was approved by the Ethics Committee of Shuyang Hospital (SYXRMYY2020KY006).

Acknowledgment

Not applicable.

Funding

This work was supported by The fifth "333 Project" training fund of Jiangsu Province (BRA2019231).

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Liu Y, Li Y, Zhan M, Liu Y, Li Z, Li J, *et al*. Astrocytic cytochrome P450 4A/20-hydroxyeicosatetraenoic acid contributes to angiogenesis in the experimental ischemic stroke. Brain Research. 2019; 1708: 160–170.

[2] Wilkins SS, Akhtar N, Salam A, Bourke P, Joseph S, Santos M, *et al*. Acute Post Stroke Depression at a Primary Stroke Center in the Middle East. PloS One. 2018; 13: e0208708.

[3] Linfante I, Nogueira RG, Zaidat OO, Arthur AS, Klucznik RP, Mack WJ, *et al*. A joint statement from the Neurointerventional Societies: our position on operator experience and training for stroke thrombectomy. Journal of NeuroInterventional Surgery. 2019; 11: 533–534.

[4] Zhang H, Masoudi FA, Li J, Wang Q, Li X, Spertus JA, *et al*. National assessment of early beta-blocker therapy in patients with acute myocardial infarction in China, 2001–2011: The China Patient-Centered Evaluative Assessment of Cardiac Events (PEACE)—Retrospective AMI Study. American Heart Journal. 2015; 170: 506–515.e1.

[5] Dávalos A, Castillo J. Progressing Stroke. Current Review of Cerebrovascular Disease. 2001; 7: 169–181.

[6] Liu D, Sun W, Scalzo F, Xiong Y, Zhang X, Qiu Z, *et al*. Early Magnetic Resonance Imaging Predicts Early Neurological Deterioration in Acute Middle Cerebral Artery Minor Stroke. Journal of Stroke and Cerebrovascular Diseases: The Official Journal of National Stroke Association. 2016; 25: 469–474.

[7] Sasaki T, Yasuda T, Abe D, Miyano R, Kainaga M, Tomura N, *et al*. A Case of Multiple Cerebral Infarction Preceding Acute Exacerbation of Idiopathic Thrombocytopenic Purpura. Journal of Stroke and Cerebrovascular Diseases: The Official Journal of National Stroke Association. 2019; 28: 789–791.

[8] Lou Y, Guo F, Liu F, Gao F, Zhang P, Niu X, *et al*. MiR-210 activates notch signaling pathway in angiogenesis induced by cerebral ischemia. Molecular and Cellular Biochemistry. 2012; 370: 45–51.

[9] Liang Y, Wu J, Liu J, Liu H, Chen J. The Clinical Implications of Thrombelastography in the Diagnosis of Acute Cerebral Infarction. Clinical Laboratory. 2018; 64: 147–152.

[10] Vallance P, Leone A, Calver A, Collier J, Moncada S. Accumulation of an endogenous inhibitor of nitric oxide synthesis in chronic renal failure. Lancet (London, England). 1992; 339: 572–575.

[11] Ogawa T, Kimoto M, Sasaoka K. Purification and properties of a new enzyme, NG,NG-dimethylarginine dimethylaminohydrolase, from rat kidney. The Journal of Biological Chemistry. 1989; 264: 10205–10209.

[12] Zakrzewicz D, Eickelberg O. From arginine methylation to ADMA: a novel mechanism with therapeutic potential in chronic lung diseases. BMC Pulmonary Medicine. 2009; 9: 5.

[13] Pekarova M, Kubala L, Martiskova H, Bino L, Twarogova M, Klinke A, *et al*. Asymmetric dimethylarginine regulates the lipopolysaccharide-induced nitric oxide production in macrophages by suppressing the activation of NF-kappaB and iNOS expression. European Journal of Pharmacology. 2013; 713: 68–77.

[14] Mittermayer F, Krzyzanowska K, Exner M, Mlekusch W, Amighi J, Sabeti S, *et al*. Asymmetric Dimethylarginine Predicts Major Adverse Cardiovascular Events in Patients with Advanced Peripheral Artery Disease. Arteriosclerosis, Thrombosis, and Vascular Biology. 2006; 26: 2536–2540.

[15] Zhang F, Li X, Dong Q, Wang Y, Zhang H. Risk of acute cerebral infarction and plasma asymmetrical dimethylarginine and homocysteine levels: a clinical correlation analysis of Chinese population. Journal of Stroke and Cerebrovascular Diseases: The Official Journal of National Stroke Association. 2014; 23: 2225–2232.

[16] Kargiotis O, Tsivgoulis G. The 2020 breakthroughs in early secondary prevention: dual antiplatelet therapy versus single antiplatelet therapy. Current Opinion in Neurology. 2021; 34: 45–54.

[17] Cerebrovascular Disease Group, Neurological Branch, Chinese Medical Association, Chinese Medical Association. Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2014. Hubei Rehabilitation Medical Association Hubei Rehabilitation Medical Association. 2015; 48: 246–257.

[18] Dumanian GA, Potter BK, Mioton LM, Ko JH, Cheesborough JE, Souza JM, *et al*. Targeted Muscle Reinnervation Treats Neuroma and Phantom Pain in Major Limb Amputees: A Randomized Clinical Trial. Annals of Surgery. 2019; 270: 238–246.

[19] Hind CR, Thomson SP, Winearls CG, Pepys MB. Serum C-reactive protein concentration in the management of infection in patients treated by continuous ambulatory peritoneal dialysis. Journal of Clinical Pathology. 1985; 38: 459–463.

[20] Smith CJ, Emsley HC, Vail A, Georgiou RF, Rothwell NJ, Tyrrell PJ, *et al*. Variability of the systemic acute phase response after ischemic stroke. Journal of the Neurological Sciences. 2006; 251: 77–81.

[21] Prokhorov AV, Hudmon KS, Marani S, Foxhall L, Ford KH, Luca NS, *et al*. Engaging physicians and pharmacists in providing smoking cessation counseling. Archives of Internal Medicine. 2010; 170: 1640–1646.

[22] Sydow K, Münzel T. ADMA and oxidative stress. Atherosclerosis Supplements. 2003; 4: 41–51.

[23] Febbraio MA, Ott P, Nielsen HB, Steensberg A, Keller C, Krustrup P, *et al*. Hepatosplanchnic clearance of interleukin-6 in humans during exercise. American Journal of Physiology. Endocrinology and Metabolism. 2003; 285: E397–E402.

[24] Bai Y, Sun L, Du L, Zhang T, Xin W, Lan X, *et al*. Association of circulating levels of asymmetric dimethylarginine (ADMA) with carotid intima-media thickness: evidence from 6168 participants. Ageing Research Reviews. 2013; 12: 699–707.

[25] Wang F, Xiong R, Feng S, Lu X, Li H, Wang S. Association of Circulating Levels of ADMA with Carotid Intima-Media Thickness in Patients with CKD: A Systematic Review and Meta-Analysis. Kidney & Blood Pressure Research. 2018; 43: 25–33.

[26] Wanby P, Teerlink T, Brudin L, Brattström L, Nilsson I, Palmqvist P, *et al*. Asymmetric dimethylarginine (ADMA) as a risk marker for stroke and TIA in a Swedish population. Atherosclerosis. 2006; 185: 271–277.

[27] Scherbakov N, Sandek A, Martens-Lobenhoffer J, Kung T, Turhan G, Liman T, *et al*. Endothelial dysfunction of the peripheral vascular bed in the acute phase after ischemic stroke. Cerebrovascular Diseases (Basel, Switzerland). 2012; 33: 37–46.

[28] Kolakowska U, Kuroczycka-Saniutycz E, Olanski W, Wasilewska A. Correlation of Salusin Beta with hs-CRP and ADMA in Hypertensive Children and Adolescents. Current Pharmaceutical Design. 2018; 24: 3551–3557.