Serum Rheumatoid Factor Levels at Acute Phase of Ischemic Stroke are Associated with Poststroke Cognitive Impairment

Zhengbao Zhu, MD,*,† Lihua Chen, MD, PhD,* Daoxia Guo, MD,* Chongke Zhong, MD,*,† Aili Wang, PhD,* Xiaoqing Bu, MD, PhD,*,† Tan Xu, MD, PhD,* Jianhui Zhang, MD,‡ Zhong Ju, MD,§ Libing Guo, MD,‖ Jintao Zhang, MD,¶ Dong Li, MD,# Chung-Shiuan Chen, MS,† Jing Chen, MD, MS,†,** Yonghong Zhang, MD, PhD,* and Jiang He, MD, PhD†,**

Background: The effect of serum rheumatoid factor (RF) on poststroke cognitive impairment remains unknown. We aimed to investigate the association of serum RF in the acute phase with cognitive impairment at 3 months after ischemic stroke onset. *Methods*: Our study was based on a random sample from the China Antihypertensive Trial in Acute Ischemic Stroke, a total of 582 patients from 7 of 26 participating sites of the trial with serum RF levels were included in this analysis. Cognitive impairment was defined as Mini-Mental State Examination less than 27 or Montreal Cognitive Assessment less than 25. *Results*: According to Mini-Mental State Examination score, the multivariate-adjusted odds ratio and 95% confidence interval of cognitive impairment for the highest tertile of serum RF was 1.79 (1.08-2.99) compared with the lowest tertile. Each standard deviation increase of log-transformed RF was associated with 33% (95% confidence interval: 7%-66%) increased risk of cognitive impairment, and a linear association between serum RF and risk of poststroke cognitive impairment was observed (P for linearity $< .01$). Adding log-transformed RF to a model containing conventional risk factors improved the predictive power for poststroke cognitive impairment (net reclassification improvement: 26.21%, $P < .01$; integrated discrimination index: 1.24%, $P = .02$). Similar significant findings were observed when cognitive function was defined by Montreal Cognitive Assessment score. *Conclusions*: Elevated serum RF levels in the acute phase were independently associated with 3-month cognitive impairment among ischemic stroke patients. Further studies are needed to replicate our findings and to clarify the potential mechanisms.

Key Words: Rheumatoid factor—ischemic stroke—cognitive impairment—risk factors—prognosis

From the *Department of Epidemiology, School of Public Health and Jiangsu Key Laboratory of Preventive and Translational Medicine for Geriatric Diseases, Medical College of Soochow University, Suzhou, China; †Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana; ‡Department of Neurology, Tongliao Municipal Hospital, Inner Mongolia, China; §Department of Neurology, Kerqin District First People's Hospital of Tongliao City, Inner Mongolia, China; ‖Department of Neurology, Siping Central Hospital, Jilin, China; ¶Department of Neurology, the 88th Hospital of PLA, Shandong, China; #Department of Internal Medicine, Feicheng City People's Hospital, Shandong, China; and **Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana.

Received November 21, 2018; revision received December 28, 2018; accepted December 31, 2018.

Grant support: This study was supported by the National Natural Science Foundation of China (grants: 81320108026 and 81673263), China Scholarship Council (grant: 201806920079), Postgraduate Research & Practice Innovation Program of Jiangsu Province (grant: KYCX18_2539), and a Project of the Priority Academic Program Development of Jiangsu Higher Education Institutions, China; Tulane University and Collins C. Diboll Private Foundation, both in New Orleans, Louisiana.

Address correspondence to Yonghong Zhang, MD, PhD, Department of Epidemiology, School of Public Health and Jiangsu Key Laboratory of Preventive and Translational Medicine for Geriatric Diseases, Medical College of Soochow University, 199 Renai Road, Industrial Park District, Suzhou, Jiangsu Province 215123, China; Jiang He, MD, PhD, Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA 70112. E-mails: yhzhang@suda.edu.cn, jhe@tulane.edu.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.12.049

Introduction

Stroke is the leading cause of long-term disability and the second leading cause of death worldwide.[1] Due to the shared pathophysiologic mechanisms between cognitive impairment and cerebrovascular disease,[2] cognitive impairment is a common complication of stroke and the prevalence of poststroke cognitive impairment is nearly 81% in China.[3] Cognitive impairment can cause disability with major impacts on quality of life and has indirect effects on functional recovery after stroke through poor adherence to treatment guidelines.[4] Therefore, in order to improve early prevention of poststroke cognitive impairment through aggressive monitoring and therapeutic interventions, it is urgent to discover some novel biomarkers to identify patients at high risk of cognitive impairment after stroke onset.

Rheumatoid factor (RF) is an autoantibody targeting the Fc region of IgG antibodies, which is most widely used in the classification of rheumatoid arthritis (RA).[5] Recently, an association between elevated RF concentration and increased mortality has been described in RA patients[6] and in a general population.[7] Apart from that, RF was reported to be associated with atherosclerosis in a community-based non-RA cohort,[8] indicating that RF might play a role in the pathogenesis of atherosclerosis. In terms of stroke, some studies had demonstrated that the risk of stroke was increased in RA patients compared with general population,[9,10] and RA was also associated with poor functional outcome[11] and increased mortality[9] after stroke onset. However, the association between serum RF and poststroke cognitive impairment remains unclear, and the curve of relationship between them also deserves to be studied. We aim to investigate the pattern and magnitude of association between serum RF and subsequent cognitive impairment after ischemic stroke among patients from the China Antihypertensive Trial in Acute Ischemic Stroke (CATIS).

Methods

Study Patients

This prospective observational study was based on a preplanned ancillary study, which was designed to investigate the effects of early blood pressure (BP) reduction on cognitive function at 3 months after randomization among a random sample of CATIS trial. Details on the rationale, design, and major results of both studies have been reported previously.[12,13] Briefly, CATIS was a multicenter, single-blind, blinded end points randomized clinical trial conducted in 26 hospitals across China.[12] From August 2009 to May 2013, a total of 4071 patients aged over 22 years who had first-ever ischemic stroke confirmed by computed tomography or magnetic resonance imaging of the brain within 48 hours of symptom onset, and with an elevated systolic BP between 140 mm Hg and 220 mm Hg were recruited. Patients with a systolic BP greater than or equal to 220 or diastolic BP greater than or equal to 120 mm Hg, severe heart failure, acute myocardial infarction or unstable angina, atrial fibrillation, aortic dissection, cerebrovascular stenosis (≥70%), resistant hypertension, coma, and treatment with intravenous thrombolytic therapy were excluded.

In the preplanned ancillary study, 660 CATIS trial participants were systemically selected prior to randomization from seven participating hospitals for cognitive function assessment at their 3-month follow-up visit.[13] The exclusion criteria for the ancillary study were visual or hearing impairment substantial enough to hinder performance on cognitive testing. Each of the 7 participating hospitals recruited 80-100 patients consecutively. The recruitments were completed by November 2012. At the 3-month visit, 15 patients were lost to follow-up and 7 patients were deceased. A total of 638 patients completed the cognitive function tests at 3 months. Trained neurologists who were unaware of treatment assignment made an appointment with patients to assess their cognitive function in the hospital or at the patient's home. Cognitive function assessment was conducted by face to face using Mini-Mental State Examination (MMSE)[14] and Montreal Cognitive Assessment (MoCA)[15] in Chinese. For present study, a further 56 patients were excluded because we did not have their blood samples. Finally, 582 participants were included in this analysis (Supplemental Figure 1).

This study was approved by the institutional review boards at Soochow University in China and Tulane University in the United States, as well as ethical committees at the participating hospitals. Written consent was obtained from all study participants or their immediate family members.

Data Collection

Baseline data on demographic characteristics, clinical features, and medication history were collected at the time of enrollment. The National Institutes of Health Stroke Scale was used to evaluate stroke severity.[16] According to the symptoms and imaging data of the patients, ischemic stroke was classified as large artery atherosclerosis, cardiac embolism, and small artery occlusion lacunae.[17] Three BP measurements were obtained at baseline by trained nurses while the patient was in the supine position using a standard mercury sphygmomanometer. The mean of the 3 BP records was used in analyses.

Serum RF Measurement

Blood samples were collected after at least 8 hours of fasting within 24 hours of hospital admission. All serum samples were separated and frozen at −80°C in the Central Laboratory of School of Public Health in Soochow University until laboratory testing. Serum RF was measured with the immunological transmission turbidimetry using a Cobas c 501 automatic biochemical analyzer (Roche, Basel, Switzerland). Intra- and interassay coefficients of variation were 3.0% and 5.0%, respectively.

Laboratory technicians who performed these measurements were blind to the clinical characteristics and outcomes of the study participants.

Outcome Assessment

The primary outcome for this ancillary study was cognitive impairment at 3 months using MMSE[14] and MoCA.[15] The MMSE contains 20 items that test cognitive performance in domains including orientation, registration, attention and calculation, recall, language, and visual construction.[14] The MoCA is a 30-item test that evaluates the following 7 cognitive domains: visuospatial/executive functions, naming, memory, attention, language, abstraction, and orientation.[15] One additional point was added to the MoCA score for participants with education less than 12 years.[15] Both MMSE and MoCA have been translated into Chinese and validated as a screening tool for cognitive impairment and dementia in the Chinese population. According to the recommended cutoffs, cognitive function was categorized as follows: 0-22 (severe cognitive impairment), 23-26 (mild cognitive impairment), and 27-30 (no cognitive impairment) for MMSE scores; 0-19 (severe cognitive impairment), 20-24 (mild cognitive impairment), and 25-30 (no cognitive impairment) for MoCA scores.[18,19] In this analysis, a score of less than 27 on the MMSE[18-20] and less than 25 on the MoCA[18,21] indicated cognitive impairment.

Statistical Analysis

All participants were categorized into 3 groups according to tertiles of serum RF levels. Baseline characteristics were presented and compared among the 3 groups. Tests for linear trend were performed using covariance analysis for continuous variables, and chi-square trend analysis for categorical variables. Logistic regression models were used to assess the association between baseline serum RF levels and subsequent cognitive impairment, and odds ratio (OR) and 95% confidence interval (CI) were calculated. Serum RF was modeled in terms of OR across tertiles and also per one standard deviation (SD) increment of log-transformed RF level. We performed 3 multiple-adjusted logistic regression models. Model 1 adjusted for age, sex, and education. Model 2 included the factors in model 1 as well as time from onset to randomization, current smoking, alcohol drinking, systolic BP, blood glucose, body mass index, baseline National Institutes of Health Stroke Scale scores, antihypertensive treatment, and hypoglycemic treatment during hospitalization. Model 3 included the factors in model 2 as well as medical history (hypertension, diabetes mellitus, hyperlipidemia, and coronary heart disease), family history of stroke, and ischemic stroke subtype. The effect of serum RF on cognitive impairment severity was analyzed using ordinal logistic regression model adjusted for the aforementioned variables. To assess the robustness of these associations, sensitivity analyses were conducted by further adjusting for serum high-sensitivity C-reactive protein in the multiple-adjusted models, or excluding patients using antihypertensive medications or lipid-lowering drugs before stroke onset to eliminate the potential effects of these factors on the relationship between serum RF and cognitive impairment.

In the secondary analyses, spline regression models were used to provide more precise estimates and explore the shape of association between serum RF and cognitive impairment, fitting a restricted cubic spline function with 4 knots placed at the 5th, 35th, 65th, and 95th percentiles of RF.[22] Furthermore, we calculated the continuous net reclassification index (NRI) and integrated discrimination improvement (IDI) to evaluate the incremental predictive value of serum RF levels in the risk of subsequent cognitive impairment based on conventional model.[23] Two-tailed $P < .05$ was considered to be statistically significant. All analyses were conducted using SAS statistical software (version 9.4, Cary, NC).

Results

Baseline Characteristics

Most baseline characteristics were well balanced between patients who were enrolled and those who were excluded in the present study (Supplemental Table 1). A total of 582 patients (405 males and 177 females) were included in the current analysis and the average age was 60 years old, with a range from 30 to 88 years. Baseline characteristics were balanced between the 3 groups by tertiles of serum RF levels (Table 1).

Association Between Baseline Serum RF and Subsequent Cognitive Impairment

At 3-month follow-up, the median (interquartile range) scores of MMSE and MoCA were 26 (22-29) and 22 (18-26), respectively. Patients in the third tertile of serum RF had the highest incidence of cognitive impairment according to either MMSE or MoCA score (Table 2).

According to MMSE score at 3 months, a total of 308 patients had cognitive impairment, among which 151 were mild cognitive impairment and 157 were severe cognitive impairment. After adjustment for potential confounders, the OR of cognitive impairment associated with the highest tertile of serum RF was 1.79 (95% CI, 1.08-2.99; $P_{trend} = .03$). On continuous analysis, each SD increase of log-transformed RF was associated with 33% (95% CI: 7%-66%) increased risk of cognitive impairment. Moreover, multivariable ordinal logistic regression analysis showed a significant association between each SD increase of log-transformed RF and cognitive impairment severity (OR, 1.23; 95% CI, 1.02-1.49; $P = .03$).

In terms of MoCA score at 3 months, 376 patients had cognitive impairment (175 were mild cognitive impairment and 201 were severe cognitive impairment). The participants in the third tertile had a significant

Table 1. *Baseline characteristics of study participants according to serum rheumatoid factor tertiles*

Characteristics*	Total	Rheumatoid factor (RF), IU/mL			
		<1.11	1.11-7.61	≥7.61	*P* value for trend
Number of subjects	582	192	192	198	
Demographics					
Age, years	60.5 ± 10.4	59.7 ± 10.2	60.4 ± 10.4	61.5 ± 10.5	0.10
Male	405 (69.6)	132 (68.8)	134 (69.8)	139 (70.2)	0.76
Education, years	7.7 ± 4.1	8.2 ± 3.9	7.2 ± 4.2	7.7 ± 4.1	0.17
Current cigarette smoking	220 (37.8)	74 (38.5)	81 (42.2)	65 (32.8)	0.24
Current alcohol drinking	196 (33.7)	65 (33.9)	65 (33.9)	66 (33.3)	0.91
Clinical features					
Time from onset to randomization, h	10.0 (5.0-24.0)	11.7 (5.0-24.0)	12.0 (5.0-24.0)	8.6 (4.0-24.0)	0.26
Systolic BP, mm Hg	167.3 ± 16.6	167.0 ± 15.6	168.0 ± 17.6	166.8 ± 16.6	0.94
Diastolic BP, mm Hg	98.3 ± 10.0	98.8 ± 9.8	98.4 ± 10.1	97.6 ± 10.2	0.26
Blood glucose, mmol/L	5.8 (5.1-7.2)	5.8 (5.1-7.0)	5.7 (5.1-7.0)	5.7 (5.1-7.3)	0.94
Body mass index, kg/m^2	24.9 ± 3.1	25.1 ± 2.7	24.7 ± 3.4	24.8 ± 3.1	0.51
Baseline NIHSS score	4.0 (3.0-7.0)	4.0 (2.0-7.0)	4.0 (2.5-7.0)	5.0 (3.0-8.0)	0.06
Medical history					
History of hypertension	448 (77.0)	159 (82.8)	142 (74.0)	147 (74.2)	0.05
History of hyperlipidemia	42 (7.2)	17 (8.9)	10 (5.2)	15 (7.6)	0.63
History of diabetes mellitus	97 (16.7)	37 (19.3)	35 (18.2)	25 (12.6)	0.08
History of coronary heart disease	61 (10.5)	16 (8.3)	21 (10.9)	24 (12.1)	0.22
Family history of stroke	96 (16.5)	30 (15.6)	34 (17.7)	32 (16.2)	0.89
Ischemic stroke subtype†					
Thrombotic	371 (63.8)	127 (66.2)	125 (65.1)	119 (60.1)	0.21
Embolic	23 (4.0)	7 (3.7)	8 (4.2)	8 (4.0)	0.84
Lacunar	197 (33.9)	64 (33.3)	61 (31.8)	72 (36.4)	0.52
Treatment during hospitalization					
Antihypertensive treatment	282 (48.5)	98 (51.0)	88 (45.8)	96 (48.5)	0.62
Hypoglycemic treatment	97 (16.7)	39 (20.3)	32 (16.7)	26 (13.1)	0.06

Abbreviations: BP, blood pressure; NIHSS, National Institute of Health Stroke Scale.
*Continuous variables are expressed as mean ± standard deviation, or as median (interquartile range). Categorical variables are expressed as frequency (percent).
†Nine patients with thrombotic and lacunar subtypes; 1 patient with all 3 subtypes.

increased risk of cognitive impairment (adjusted OR, 2.08; 95% CI, 1.20-3.60; P_{trend} = .01) compared to those in the lowest tertile of RF, and each SD increase of log-transformed RF was associated with 37% (95% CI: 8%-73%) increased risk of cognitive impairment. Similarly, there was a significant association between each SD increase of log-transformed RF and cognitive impairment severity (OR, 1.24; 95% CI, 1.03-1.50; *P* = .02).

In the sensitivity analyses, after adjusting for serum high-sensitivity C-reactive protein in the multiple-adjusted models, or excluding the participants using antihypertensive medications or lipid-lowering drugs before stroke onset, the association between baseline serum RF concentrations and subsequent cognitive impairment remained significant (Supplemental Table 2).

The Curve of Association Between Serum RF and Cognitive Impairment

We used a logistic regression model with restricted cubic splines to evaluate the curve of association between baseline serum RF and subsequent cognitive impairment, and we found a positive linear dose-response relationship between them. As shown in Fig 1, A, with an increase of serum RF levels, the risk of cognitive impairment (MMSE score < 27) at 3 months after stroke onset increased (*P* for nonlinearity = .50; *P* for linearity < .01). Similarly, the risk of 3-month cognitive impairment (MoCA score < 25) increased with an increase in baseline serum RF levels (Fig 1, B; *P* for nonlinearity = .17; *P* for linearity = .02).

Incremental Discriminatory Ability of Serum RF for Cognitive Impairment

We examined whether adding serum RF to the conditional logistic regression model consisting of conventional risk factors improved the discriminatory abilities for the risk of subsequent cognitive impairment among patients with acute ischemic stroke. As shown in Table 3, adding baseline log-transformed RF to the conventional model significantly improved the discriminatory ability for 3-month cognitive impairment (MMSE score < 27:

Table 2. *Odds ratios and 95% confidence intervals for the risk of cognitive impairment* according to rheumatoid factor tertiles*

	Rheumatoid factor (RF), IU/mL			*P* value for trend	Each SD (0.54, IU/mL) increase in log-RF
	<1.11	1.11-7.61	≥7.61		
MMSE score <27, n (%)	94 (49.0)	91 (47.4)	123 (62.1)		308 (52.9)
Model 1	1.00	0.92 (0.61-1.40)	1.63 (1.08-2.48)	0.02	1.21 (1.02-1.44)
Model 2	1.00	0.95 (0.58-1.55)	1.81 (1.09-2.98)	0.02	1.35 (1.09-1.68)
Model 3	1.00	0.92 (0.56-1.51)	1.79 (1.08-2.99)	0.03	1.33 (1.07-1.66)
MMSE categories, n (%)†					
None (27-30)	98 (51.0)	101 (52.6)	75 (37.9)		274 (47.1)
Mild (23-26)	46 (24.0)	42 (21.9)	63 (31.8)		151 (26.0)
Severe (0-22)	48 (25.0)	49 (25.5)	60 (30.3)		157 (27.0)
Model 1	1.00	0.92 (0.62-1.35)	1.40 (0.96-2.05)	0.07	1.17 (1.00-1.37)
Model 2	1.00	0.93 (0.59-1.46)	1.48 (0.94-2.31)	0.08	1.24 (1.03-1.50)
Model 3	1.00	0.89 (0.56-1.40)	1.46 (0.93-2.29)	0.10	1.23 (1.02-1.49)
MoCA score <25, n (%)	114 (59.4)	119 (62.0)	143 (72.2)		376 (64.6)
Model 1	1.00	1.13 (0.74-1.72)	1.73 (1.12-2.67)	0.01	1.24 (1.04-1.49)
Model 2	1.00	1.25 (0.76-2.08)	2.01 (1.18-3.41)	0.01	1.38 (1.10-1.74)
Model 3	1.00	1.22 (0.73-2.04)	2.08 (1.20-3.60)	0.01	1.37 (1.08-1.73)
MoCA categories, n (%)†					
None (25-30)	78 (40.6)	73 (38.0)	55 (27.8)		206 (35.4)
Mild (20-24)	53 (27.6)	63 (32.8)	59 (29.8)		175 (30.1)
Severe (0-19)	61 (31.8)	56 (29.2)	84 (42.4)		201 (34.5)
Model 1	1.00	0.93 (0.64-1.36)	1.54 (1.06-2.24)	0.02	1.19 (1.02-1.39)
Model 2	1.00	0.98 (0.63-1.52)	1.67 (1.07-2.59)	0.02	1.26 (1.04-1.51)
Model 3	1.00	0.94 (0.60-1.46)	1.65 (1.05-2.58)	0.03	1.24 (1.03-1.50)

Abbreviations: MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; RF, rheumatoid factor; SD, standard deviation.

Model 1, adjusted for age, sex, and education.

Model 2, adjusted for Model 1 and further adjusted for time from onset to randomization, current smoking, alcohol drinking, systolic blood pressure, blood glucose, body mass index, baseline NIHSS scores, antihypertensive treatment and hypoglycemic treatment during hospitalization.

Model 3, adjusted for Model 2 and further adjusted for medical history (hypertension, diabetes mellitus, hyperlipidemia, and coronary heart disease), family history of stroke, and ischemic stroke subtype.

*MMSE score < 27 or MoCA score < 25 indicate cognitive impairment.

†Odds ratios are derived from ordinal regression.

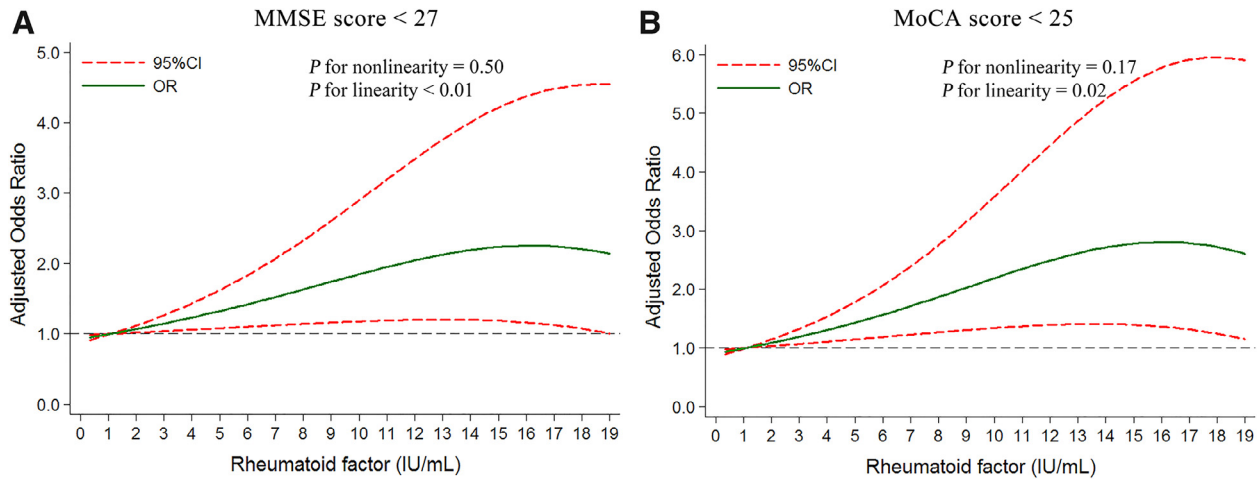

Figure 1. *Association of serum rheumatoid factor (RF) with risk of cognitive impairment after acute ischemic stroke. Odds ratios and 95% confidence intervals derived from restricted cubic spline regression, with knots placed at the 5th, 35th, 65th, and 95th percentiles of the distribution of serum RF. The reference point for serum RF is 1.11 IU/mL. Odds ratios were adjusted for the same variables as model 3 in Table 2. Panel A: MMSE score less than 27; Panel B: MoCA score less than 25.*

Table 3. *Reclassification and discrimination statistics (95% CI) for cognitive impairment* by serum RF among patients with acute ischemic stroke*

	Continuous NRI, %		IDI, %	
	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
MMSE score <27				
Conventional model	Reference		Reference	
Conventional model + log-RF	26.21 (7.79-44.62)	<0.01	1.24 (0.17-2.32)	0.02
MoCA score <25				
Conventional model	Reference		Reference	
Conventional model + log-RF	29.38 (9.88-48.88)	<0.01	1.36 (0.20-2.52)	0.02

Abbreviations: IDI, integrated discrimination index; NRI, net reclassification improvement; RF, rheumatoid factor.

Conventional model included age, sex, education, time from onset to randomization, current smoking, alcohol drinking, systolic blood pressure, blood glucose, body mass index, baseline NIHSS scores, antihypertensive treatment during hospitalization, hypoglycemic treatment during hospitalization, medical history (hypertension, diabetes mellitus, hyperlipidemia, and coronary heart disease), family history of stroke, and ischemic stroke subtype.

*MMSE score < 27 or MoCA score < 25 indicate cognitive impairment.

NRI = 26.21%, IDI = 1.24%; MoCA score < 25: NRI = 29.38%, IDI = 1.36%; all *P* value < .05).

Discussion

To our knowledge, this is the first prospective multicenter study to investigate the association between baseline serum RF concentration and cognitive impairment after acute ischemic stroke onset. In this preplanned ancillary study of CATIS, we observed a dose-response association between serum RF levels at baseline and 3-month cognitive impairment in acute ischemic stroke patients, and sensitive analyses further confirmed this finding. Furthermore, adding serum RF to conventional risk factors could improve risk prediction for the subsequent cognitive impairment.

The routine laboratory analysis of RF in clinical practice is used for classification of RA, a chronic systemic inflammatory disease which can cause significant morbidities due to synovial inflammation, joint destruction, and associated disabilities.[5] In the general population, individuals with higher RF levels were confirmed to have greater long-term risk of RA.[24] Apart from that, serum RF concentration was also reported to be associated with the risk and prognosis of cardiovascular disease. A community non-RA cohort based on Multi-Ethnic Study of Atherosclerosis revealed that serum RF levels were associated with subclinical and clinical atherosclerosis in African American women.[8] Another study conducted in entire Danish population found that the risks of atrial fibrillation and stroke increased in RA patients.[10] Similarly, Soderg-ren et al analyzed the data of northern Sweden register and observed that the incidence of stroke and the subsequent fatality were higher among RA patients compared with the general population.[9] In a large prospective cohort of 11,872 subjects, RF was associated with increased cardiovascular mortality after adjustment for cardiovascular risk factors, even in those without joint symptoms.[7] In addition, Nguyen-Oghalai et al's analysis of 47,853 stroke patients indicated that RA was associated with poor functional outcome at discharge and follow-up.[11] However, little is known about the relationship between serum RF level at admission and subsequent cognitive impairment after acute ischemic stroke.

In the present study, we investigated the association of baseline serum RF level with 3-month cognitive impairment among acute ischemic stroke patients and we found a strong dose-response relationship between them. In other words, the risk of poststroke cognitive impairment at 3 months increased with an increase of RF levels at admission, indicating that serum RF might be a valuable marker in prediction of subsequent cognitive impairment after stroke onset. As mentioned previously, intact cognitive function is critical for performing fundamental daily activities in general population. For patients with ischemic stroke, cognitive impairment has adverse effects on adhering to treatment regimens and initiating activities after stroke onset based on individual's health condition.[4] Hence, identifying biomarkers to predict cognitive impairment after ischemic stroke onset is an initial step for developing effective and targeted interventions to minimize its adverse outcomes. From the findings of our study, ischemic stroke patients with high serum RF levels should receive aggressive monitoring and therapeutic interventions to prevent subsequent cognitive impairment.

The precise mechanisms underlying the detrimental effect of elevated serum RF on cognitive function after ischemic stroke remain to be elucidated. RF is an autoantibody targeting the Fc region of IgG antibodies.[5] Animal and human studies have found that autoimmune process may play a role in the development of poststroke cognitive decline,[25] and the primary harmful mechanism of autoantibodies in the central nervous system is inhibition of signal transduction and interference with neuronal function.[26] In addition, inflammation and cardiovascular disease risk factors have been considered as the mechanisms of incident cognitive impairment and cognitive decline in the general

population.[27,28] High serum RF is well known to be associated with inflammation,[29] smoking,[30] and diabetes,[31] which may partly explain the effects of serum RF on the risk of poststroke cognitive impairment. Moreover, RF has been shown to have direct pathological effects on the endothelium through circulating immune complexes, and can lead to endothelial dysfunction[32] which is associated with subsequent infarct expansion[33] and hemorrhagic transformation,[34] thus increase the risk of poststroke cognitive impairment.

Several strengths of our study deserve to be mentioned. First, this is the first study to investigate the association between baseline serum RF and cognitive impairment after acute ischemic stroke onset. Second, this prospective study was from the CATIS randomized clinical trial with standardized protocols and rigid quality control procedures in data collection and outcome assessment. Third, comprehensive information about relevant covariates was controlled in the multivariable models, so the present study in methodology was appropriate and provide a more valid appraisal of the association between serum RF and the risk of poststroke cognitive impairment. However, some limitations should be discussed here. First, this is an observational study based on a random sample of CATIS trail, thus a selection bias might exist. This trial excluded ischemic stroke patients with BP greater than or equal to 220/120 mm Hg, severe heart failure, acute myocardial infarction or unstable angina, atrial fibrillation, aortic dissection, cerebrovascular stenosis, resistant hypertension, coma, or treatment with intravenous thrombolytic therapy at admission. Therefore, the results of present study may not be generalizable to all ischemic stroke patients. Further studies from other samples of ischemic stroke patients are needed to replicate our findings. Second, the possibility of residual confounding might not be fully eliminated in an observational study, although several important potential confounders had been controlled in the multivariable-adjusted models. Third, it was difficult to conduct the test of cognitive function in acute phase of ischemic stroke, so we had no data of participants' cognitive function at baseline and we could not control the potential confounding effect of prestroke cognitive impairment. However, the characteristics associated with cognitive function were balanced across RF tertiles at baseline and we adjusted these characteristics when we investigated the association of RF with poststroke cognitive impairment, indicating that the confounding effect of baseline cognitive function might be minimal. Finally, we did not conduct serial measurements of serum RF levels after stroke onset, so we were unable to assess the association between RF changes and poststroke cognitive impairment and further studies were needed to investigate this association.

Conclusions

In summary, we found that elevated serum RF levels in the acute phase were associated with 3-month cognitive impairment among ischemic stroke patients, independent of established conventional risk factors. Further prospective studies conducted among stroke patients with different social and cultural backgrounds are needed to replicate our findings and to clarify the potential biological mechanisms underlying this association.

Disclosure

The authors have no conflict of interest to declare.

Acknowledgments: We thank the study participants and their relatives and the clinical staff at all participating hospitals for their support and contribution to this project.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2018.12.049.

Reference

1. Donnan GA, Fisher M, Macleod M, et al. Stroke. Lancet 2008;371:1612-1623. https://doi.org/10.016/S0140-6736(08)60694-7.
2. Kalaria RN. Linking cerebrovascular defense mechanisms in brain ageing and Alzheimer's disease. Neurobiol Aging 2009;30:1512-1514. https://doi.org/10.016/j.neurobiolaging.2007.10.020. Epub 8 Jan 10.
3. Qu Y, Zhuo L, Li N, et al. Prevalence of post-stroke cognitive impairment in china: a community-based, cross-sectional study. PLoS One 2015;10:e0122864. https://doi.org/10.1371/journal.pone. eCollection 2015.
4. Cumming TB, Marshall RS, Lazar RM. Stroke, cognitive deficits, and rehabilitation: still an incomplete picture. Int J Stroke 2013;8:38-45. https://doi.org/10.1111/j.747-4949.2012.00972.x.
5. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580-1588. https://doi.org/10.136/ard.2010.138461.
6. Goodson N, Marks J, Lunt M, et al. Cardiovascular admissions and mortality in an inception cohort of patients with rheumatoid arthritis with onset in the 1980s and 1990s. Ann Rheum Dis 2005;64:1595-1601. Epub 2005 Apr 20.
7. Tomasson G, Aspelund T, Jonsson T, et al. Effect of rheumatoid factor on mortality and coronary heart disease. Ann Rheum Dis 2010;69:1649-1654. https://doi.org/10.136/ard.2009.110536. Epub 2009 Jul 23.
8. Majka DS, Vu TT, Pope RM, et al. Association of rheumatoid factors with subclinical and clinical atherosclerosis in African American Women: the multiethnic study of atherosclerosis. Arthritis Care Res 2017;69:166-174. https://doi.org/10.1002/acr.22930.
9. Sodergren A, Stegmayr B, Ohman ML, et al. Increased incidence of stroke and impaired prognosis after stroke among patients with seropositive rheumatoid arthritis. Clin Exp Rheumatol 2009;27:641-644.
10. Lindhardsen J, Ahlehoff O, Gislason GH, et al. Risk of atrial fibrillation and stroke in rheumatoid arthritis:

Danish nationwide cohort study. BMJ 2012;344:e1257. https://doi.org/10.1136/bmj.e257.
11. Nguyen-Oghalai TU, Wu H, McNearney TA, et al. Functional outcome after stroke in patients with rheumatoid arthritis and systemic lupus erythematosus. Arthritis Rheum 2008;59:984-988. https://doi.org/10.1002/art.23816.
12. He J, Zhang Y, Xu T, et al. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: the CATIS randomized clinical trial. JAMA 2014;311:479-489.
13. Bu X, Zhang Y, Bazzano LA, et al. Effects of early blood pressure reduction on cognitive function in patients with acute ischemic stroke. Int J Stroke 2016;11:1009-1019. Epub 2016 Jul 13.
14. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198.
15. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695-699. https://doi.org/10.1111/j.532-5415.2005.53221.x.
16. Brott T, Adams Jr. HP, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20:864-870.
17. Adams Jr. HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35-41.
18. Delavaran H, Jonsson AC, Lovkvist H, et al. Cognitive function in stroke survivors: a 10-year follow-up study. Acta Neurol Scand 2017;136:187-194. https://doi.org/10.1111/ane.12709. Epub 2016 Nov 1.
19. Webb AJ, Pendlebury ST, Li L, et al. Validation of the Montreal cognitive assessment versus Mini-Mental State Examination against hypertension and hypertensive arteriopathy after transient ischemic attack or minor stroke. Stroke 2014;45:3337-3342. https://doi.org/10.1161/STROKEAHA.114.006309. Epub 2014 Sep 23.
20. Pendlebury ST, Cuthbertson FC, Welch SJ, et al. Underestimation of cognitive impairment by Mini-Mental State Examination versus the Montreal Cognitive Assessment in patients with transient ischemic attack and stroke: a population-based study. Stroke 2010;41:1290-1293. https://doi.org/10.161/STROKEAHA.110.579888. Epub 2010 Apr 8.
21. Pendlebury ST, Mariz J, Bull L, et al. MoCA, ACE-R, and MMSE versus the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery after TIA and stroke. Stroke 2012;43:464-469. https://doi.org/10.1161/STROKEAHA.111.633586. Epub 2011 Dec 8.
22. Durrleman S, Simon R. Flexible regression models with cubic splines. Stat Med 1989;8:551-561.
23. Pencina MJ, D'Agostino Sr. RB, D'Agostino Jr. RB, et al. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157-172.
24. Nielsen SF, Bojesen SE, Schnohr P, et al. Elevated rheumatoid factor and long term risk of rheumatoid arthritis: a prospective cohort study. BMJ 2012;345:e5244. https://doi.org/10.1136/bmj.e5244.
25. Doyle KP, Buckwalter MS. Does B lymphocyte-mediated autoimmunity contribute to post-stroke dementia? Brain Behav Immun 2017;64:1-8. https://doi.org/10.1016/j.bbi.2016.08.009. Epub Aug 13.
26. Vincent A, Bien CG, Irani SR, et al. Autoantibodies associated with diseases of the CNS: new developments and future challenges. Lancet Neurol 2011;10:759-772. https://doi.org/10.1016/S474-4422(11)70096-5.
27. Gimeno D, Marmot MG, Singh-Manoux A. Inflammatory markers and cognitive function in middle-aged adults: the Whitehall II study. Psychoneuroendocrinology 2008;33:1322-1334. https://doi.org/10.016/j.psyneuen.2008.07.006. Epub Sep 5.
28. Meyer JS, Rauch GM, Rauch RA, et al. Cardiovascular and other risk factors for Alzheimer's disease and vascular dementia. Ann N Y Acad Sci 2000;903:411-423.
29. Hughes-Austin JM, Deane KD, Derber LA, et al. Multiple cytokines and chemokines are associated with rheumatoid arthritis-related autoimmunity in first-degree relatives without rheumatoid arthritis: Studies of the Aetiology of Rheumatoid Arthritis (SERA). Ann Rheum Dis 2013;72:901-907. https://doi.org/10.1136/annrheumdis-2012-201505. Epub 2012 Aug 21.
30. Jonsson T, Thorsteinsson J, Valdimarsson H. Does smoking stimulate rheumatoid factor production in non-rheumatic individuals? APMIS 1998;106:970-974.
31. Onat A, Ademoglu E, Can G, et al. Rheumatoid factor mediates excess serum lipoprotein(a) for independent association with type 2 diabetes in men. Anatol J Cardiol 2015;15:782-788. https://doi.org/10.5152/akd.2014.5826. Epub 2014 Oct 31.
32. Kato H, Yamakawa M, Ogino T. Complement mediated vascular endothelial injury in rheumatoid nodules: a histopathological and immunohistochemical study. J Rheumatol 2000;27:1839-1847.
33. Yagita Y, Kitagawa K, Sasaki T, et al. Rho-kinase activation in endothelial cells contributes to expansion of infarction after focal cerebral ischemia. J Neurosci Res 2007;85:2460-2469.
34. Wang W, Li M, Chen Q, et al. Hemorrhagic transformation after tissue plasminogen activator reperfusion therapy for ischemic stroke: mechanisms, models, and biomarkers. Mol Neurobiol 2015;52:1572-1579. https://doi.org/10.007/s12035-014-8952-x. Epub 2014 Nov 4.