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ASSOCIATION OF ASPIRIN RESISTANCE WITH INCREASED MORTALITY IN ISCHEMIC STROKE

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Abstract: *Objective:* To investigate the association of aspirin resistance (AR) with mortality in a cohort of Chinese patients with acute ischemic stroke (AIS). *Methods:* One hundred and ninety-six ischemic stroke patients who received at least 7 days of aspirin therapy prior to stroke onset were enrolled. The outcome measure was all-cause and cardiovascular disease (CVD) mortality at 1-year follow-up. The relation of AR with the two end points was investigated with the use of logistic regression models. *Results:* The median age of included patients was 65(IQR, 56-76) years and 82(41.8%) were female. Thirty-five patients were defined as AR; thus, the rate was 17.9% (95%CI, 12.5% to 23.2%). The median NIHSS score was significantly higher in patients with AR than those with AS [12 (IQR, 10-17) vs. 7 (IQR, 4-10); Z=5.188; P<0.001]. Similarly, the median infarct volume was also significantly higher in AR than in AS [18.8 (IQR, 4.3-25.2) ml vs. 13.2 (IQR, 3.3-18.7) ml; Z=3.322; P=0.008]. During follow-up there were 43 patients (21.9%) died, including 24 CVD mortality (12.2%). In univariate logistic regression analysis, we found that the rate of all-cause mortality and CVD mortality increased by 390% (OR=4.90; 95%CI:2.24-10.75) and 422% (OR=5.22; 95%CI, 2.10-12.98) in AR group. After adjusting for all other significant predictors, AR still associated with high mortality and the rate of all-cause mortality and CVD mortality increased by 215% (OR=3.15; 95%CI:1.88-4.93) and 231% (OR=3.31; 95%CI, 1.96-522), respectively. *Conclusions:* The present study shows that AR was a useful prognostic marker of all-cause or CVD mortality in Chinese patients with AIS.

Key words: Aspirin resistance, ischemic stroke, mortality, cardiovascular disease.

Introduction

Stroke is a leading cause of death and disability in China (1). Aspirin is the most commonly used antiplatelet drug in both primary and secondary prevention of cerebrovascular and cardiovascular diseases (2). There is no debate that long term aspirin use attenuates the risks of myocardial infarction, stroke, and vascular related deaths in patients with cardiovascular disease (3). A previous study confirmed that aspirin therapy was associated with the 34% reduction in nonfatal myocardial infarction, 25% reduction in nonfatal stroke, and 18% reduction in all-cause mortality (4).

A proportion of patients may have stroke recurrence while they are on treatment with aspirin, giving rise to term aspirin resistance or aspirin failure. Studies have suggested that such recurrence could partly be attributed to biochemical aspirin resistance (AR, 2). In a Chinese cohort, Zhang et al. (5) reported that patients with AR may have a greater risk of suffering stroke recurrence events. Similarly, another study suggested that AR in the acute stage was associated with early radiological events, including new ischemic lesions (6).

Snoep et al. (7) found that patients with AR exhibit an increased risk of recurrent cardiovascular events compared with patients with aspirin sensitive. Yi et al. (8) reported that stroke patients with AR were at a greater risk of clinically important vascular events. Furthermore, a previous study showed that patients who are resistant to aspirin are at a greater risk of clinically important cardiovascular morbidity long term than patients who are sensitive to aspirin (9). We hypothesized that AR is risk factor for mortality in patients with ischemic stroke. The aim of this study is to determine aspirin reaction units (ARU) at admission, and investigate the association of AR with mortality in a cohort of Chinese patients with acute ischemic stroke (AIS).

Patients and Methods

Ethics

This study was approved by the investigational review board of the Central hospital of Zhoukou according to Helsinki Declaration. All methods were performed in accordance with the relevant guidelines. The patients or their relatives gave written informed consents prior to entering the study.

Patients

From January 2016 to June 2017, consecutive first-ever ischemic stroke patients without any pre-morbid handicap were identified. The inclusion criteria were (1) at least 7 days of aspirin therapy (acetylsalicylic acid, 100 mg daily) prior to stroke onset; (2) within 24 hours of experiencing a new focal or global neurological event; (3) evidence of ischemic infarct on magnetic resonance imaging (MRI); (4) with informed consents and finished follow-up. Patients with the following criteria: (1) malignant tumor; (2) liver and kidney function insufficiency; (3) Other neurological diseases (such as Intracerebral hemorrhage, cerebral hemorrhage, Parkinson's Disease and Alzheimer's Disease) were excluded. In addition, patients who lost blood samples, had platelet function disorders or

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concurrently taking an additional anti-platelet or anticoagulant also had been excluded.

Clinical variables

Demographic data (age and sex) and vascular risk factors [hypertension, diabetes mellitus, hypercholesterolemia, coronary heart diseas, a history of transient ischemic attack (TIA) and family history of stroke] were obtained at admission. Pre-stroke therapy (including antiplatelet agents, antihypertensive treatment and statins) and acute treatment (IV thrombolysis and/or mechanical thrombectomy) was recorded. Patients were evaluated with the National Institute of Health Stroke Scale (NIHSS) (10) score at their admission, performed by a stroke neurologist certified. The patients were classified according to the criteria of the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification. Brain imaging (MRI) was done routinely within 24 hours after admission. Diffusion-weighted imaging (DWI) was available. The infarct volume was calculated by using the formula $0.5 \times a \times b \times c$ (where a is the maximal longitudinal diameter, b is the maximal transverse diameter perpendicular to a, and c is the number of 10-mm slices containing infarct) (11).

Laboratory testing

In this study, 3ml fasting blood samples were drawn into tubes containing 3.2% citrate at first morning after admission. Aspirin-induced platelet inhibition was measured using a commercially available point-of-care device, the Ultegra Rapid Platelet Function Assay-ASA (the VerifyNow System, Accumetrics, San Diego, California). The result is expressed in aspirin reaction units (ARU). The AR was defined as the ARU greater than or equal 550 (12). An ARU value of ≥550 IU was defined as AR, while <550IU was defined as aspirin sensitive (AS). Results of the other blood analyses, such as C-reactive protein (CRP), fasting blood glucose (FBG), Platelet (PLT) and white blood count (WBC) were also measured using routine laboratory methods.

End Points and follow-up

The primary outcome measure was all-cause mortality at 1-year follow-up. Causes of death were coded centrally by trained coders by use of the International Statistical Classification of Diseases and Related Health Problems, 10th revision. All deaths were identified from death certificates that were confirmed by authorized physicians only. Death was also assessed by Cardiovascular Disease (CVD) death (including coronary heart disease [CHD] death, congestive heart failure (CHF) death, fatal stroke death, or other cardiovascular death). CVD death was defined according to the Academic Research Consortium criteria (13). The follow-up protocol after hospital discharge included phone interviews at 1 month, 6 months, 1 year thereafter to ascertain vital status and occurrence of cardiovascular events.

Statistical analysis

Results were expressed as n (%) for categorical variables and as medians (interquartile ranges, IQRs) for the continuous variables. Univariate data on demographic and clinical features were compared by Mann-Whitney U-test or Chi-Square test as appropriate. The relation of AR with the two end points was investigated with the use of logistic regression models. We used crude models and multivariate models adjusted for all significant outcome predictors confirmed in the univariate analysis and report odds ratios (ORs).

Second, receiver operating characteristic curves (ROC) was used to test the overall predict accuracy of AR, and results were reported as area under the curve (AUC). To test whether the AR improves score performance, we considered the two nested logistic regression models with NIHSS and AR as compared with NIHSS only. The positive predictive value (PPV), negative predictive value (NPV) and the diagnostic accordance rate were also calculated. All statistical analysis was performed with SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA) and the ROCR package (version 1.0-2). Statistical significance was defined as $P<0.05$.

Results

Patient characteristics

Finally, 196 stroke patients were included and completed 1-year follow-up. The median age of those patients was 65(IQR, 56-76) years and 82(41.8%) were female. At admission, the median NIHSS score was 8 (IQR, 5–11) and 27 patients (13.7%) received tissue plasminogen activator-treated. The raw ARUs of the included patients ranged from 360 to 656, with a median of 465 (IQR, 408-529). Thirty-five patients were defined as AR; thus, the rate was 17.9% (95%CI, 12.5% to 23.2%). The baseline characteristics of the patients are described in Table 1.

Main results

The median NIHSS score was significantly higher in patients with AR than those with AS [12 (IQR, 10-17) vs. 7 (IQR, 4-10); $Z=5.188$; $P<0.001$]. Median regression estimated a statistically significant increase in NIHSS score of 0.036 point for every 1-point increase in ARU (95% CI, 0.022 to 0.069; $P<0.001$). This corresponds to an approximate median increase of 1 point in NIHSS score for every 28-point increase in ARU. Similarly, the median infarct volume was also significantly higher in AR than in AS [18.8 (IQR, 4.3-25.2) ml vs. 13.2 (IQR, 3.3-18.7) ml; $Z=3.322$; $P=0.008$].

During follow-up there were 43 patients (21.9%, 95%CI: 16.1%-27.7%) died, including 24 CVD mortality (12.2%, 95CI%: 7.7%-16.8%). In univariate logistic regression analysis, we found that the rate of all-cause mortality and CVD mortality increased by 390% (OR=4.90; 95%CI:2.24-10.75) and 422% (OR=5.22; 95%CI, 2.10-12.98) in AR group. After adjusting for all other significant predictors, AR still associated with high

mortality and the rate of all-cause mortality and CVD mortality increased by 215% (OR=3.15; 95%CI:1.88-4.93) and 231% (OR=3.31; 95%CI, 1.96-522), respectively (Table 2).

Table 1
Baseline characteristics of stroke patients

Demographic characteristics	Patients with ischemic stroke†
N	196
Age, years	65(56-75)
Female sex	82(41.8)
BMI, kg/m2	26.8(24.3-29.1)
Median NIHSS score at admission	8(5-11)
Lesion volumes, ml	14.5(3.6-20.4)
Time from onset to ARU test, hours	14.0(6.0-18.0)
Vascular risk factors	
Hypertension	135(68.9)
Diabetes mellitus	77(39.3)
Coronary heart disease	52(26.5)
Hypercholesterolemia	61(31.1)
Family history for stroke	48(24.5)
History for TIA	39(19.9)
Pre-stroke treatment	
Antihypertensive drug	99(50.5)
Statin use	51(26.0)
Acute treatment of IV-tPA	27(13.8)
Stroke etiology	
Small-vessel occlusive	48(24.5)
Large-vessel occlusive	42(21.4)
Cardioembolic	76(38.8)
Other	18(9.2)
Unknown	12(6.1)
Laboratory findings	
ARU	465(408-529)
FBG, mmol/l	5.68(5.07-7.01)
CRP, mg/l	8.6(4.9-15.3)
WBC, X109/l	8.83(7.55-10.53)
PLT, x103/ml	201(167-249)
AR‡, n (%, 95%CI)	35(17.9%; 12.5% to 23.2%)

† results were presented as medians (IQR) or n (%); ‡ defined by more than 550 ARU. IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; BMI, body mass index; PLT, Platelet; WBC, white cell count; TPA-T: Tissue plasminogen activator-treated; CRP, C-reactive protein; FBG, fasting blood glucose; ARU, aspirin reaction units; AR, aspirin-resistant; TIA, Transient ischemic attack

The area under the ROC curve to predict all-cause mortality for AR with an AUC of 0.72 (0.62–0.82), which yielded a sensitivity of 55.8% and a specificity of 88.2% was in the range of the NIHSS with an AUC of 0.74 (0.65–0.83; P=0.09). AR could improve the NIHSS score (AUC of the combined model, 0.77; 95% CI, 0.69–0.886; P=0.03). Furthermore, patients with AR was considered as an indicator to predict all-cause mortality, the positive predictive value (PPV) and negative predictive value (NPV) were 48.6% and 81.3%, respectively. The diagnostic accordance rate was 77.6%. Similarly, with an AUC of 0.73 (95%CI: 0.64–0.83), AR show a comparable predictive value to CVD mortality when compared with NIHSS (AUC: 0.745[0.66–0.84]; P=0.10). AR was an indicator to predict CVD mortality, the positive predictive value (PPV) and negative predictive value (NPV) were 31.4% and 91.9%, respectively. The diagnostic accordance rate was 81.1%.

Discussion

AR is the inability of aspirin to reduce platelet production of thromboxane A2 and thereby platelet activation and aggregation. Increasing degrees of AR may correlate independently with increasing risk of cardiovascular events (14). In this study, we showed that AR was associated with long-term all-cause and CVD mortality in patients with ischemic stroke. Importantly, AR could improve the prognostic value of the NIHSS score. Further, AR were associated with worse neurological deficit (defined by the NIHSS and infarct size).

Consistent with our findings, Eikelboom et al. (15) reported an increased risk for cardiovascular death associated with AR in patients with cardiovascular disease or diabetes. Similarly, Wang et al. (16) showed that AR was an independent marker to predict poor functional outcome and mortality in patients with ischemic stroke. AR also had been reported associated with an increased risk of adverse clinical outcomes in stable patients with CAD (17). Furthermore, previous studies had suggested that AR was associated with an increased risk of severe stroke and large infarct volume in patients taking aspirin before stroke onset (18, 19), which confirmed by our results. In addition, Agayeva et al. (20) found that they were unable to demonstrate a substantial positive influence of pre-stroke antiplatelet usage on stroke severity.

Previous studies have reported that AR occurs in 5% to 65% of people with ischemic strokes (21). Two previous studies in Chinese stroke patients found that the rate of AR was 18.9% (16) and 20.1% (5), respectively. Similarly, in this study, 17.9% of the stroke patients were diagnosed as AR. Kim et al. (6) shown that the prevalence of AR among stroke patients was 16.3%. However, these estimates are unreliable because of the small sample sizes, different types of patients studied (different prevalence of potential confounders such as age, sex, ethnic origin, and clinical conditions), uncertainty about compliance, different definitions of aspirin resistance, lack of agreement between different tests of platelet function, and uncertainty about measurement stability over time.

Several possible biologic mechanisms might explain the association of AR with stroke mortality. First, patients with AR may lead to a larger thrombus and accumulating

Table 2
Univariate and multivariate logistic regression analysis for all-cause mortality and CVD mortality

Parameter	Univariate Analysis			Multivariate Analysis†		
	OR [a]	95% CI [a]	P	OR [a]	95% CI [a]	P
All-cause mortality						
AR VS. AS‡	4.90	2.24-10.75	< 0.001	3.15	1.88-4.93	<0.001
Sex (male vs. female)	0.86	0.63-1.29	0.72	—		
Age (increase per unit)	1.11	1.03-1.21	<0.001	1.05	1.01-1.16	0.001
Infarct volume (increase per unit)	1.22	1.09-1.33	0.002	1.10	1.01-1.23	0.013
NIHSS (increase per unit)	1.20	1.14-1.27	< 0.001	1.14	1.06-1.24	< 0.001
Hypertension	1.55	1.02-2.98	0.15	—		
Diabetes mellitus	0.79	0.48–1.30	0.34	—		
Coronary heart disease	1.10	0.65-2.11	0.83	—		
Hypercholesterolemia	0.93	0.50-1.95	0.92	—		
Family history for stroke	1.38	0.72–2.54	0.85	—		
History for TIA	1.44	0.83-2.22	0.69	—		
Pre-stroke treatment	1.20	0.75–1.99	0.48	—		
Acute treatment	0.61	0.49-0.75	<0.001	0.54	0.44-0.63	<0.001
Glucose (increase per unit)	1.03	1.01-1.09	0.006	1.01	1.00-1.04	0.010
CRP (increase per unit)	1.13	1.02-1.22	0.009	1.07	1.01-1.26	0.042
PLT (increase per unit)	1.01	0.99-1.02	0.83	—		
Small-vessel occlusive	0.77	0.39–0.94	0.043	0.85	0.53-1.16	0.26
Large-vessel occlusive	0.59	0.25–1.43	0.24	—		
Cardioembolic	1.66	0.75–2.58	0.41	—		
CVD mortality						
AR VS. AS	5.22	2.10-12.98	< 0.001	3.31	1.96-5.22	<0.001
Sex (male vs. female)	0.93	0.76-1.33	0.39	—		
Age (increase per unit)	1.06	1.04-1.09	<0.001	1.04	1.01-1.10	0.009
Infarct volume (increase per unit)	1.20	1.08-1.33	0.002	1.12	1.01-1.27	0.011
NIHSS (increase per unit)	1.16	1.12-1.22	<0.001	1.10	1.03-1.20	<0.001
Hypertension	1.83	1.13-3.04	0.15	—		
Diabetes mellitus	0.86	0.53-1.55	0.37	—		
Coronary heart disease	1.33	0.87–2.44	0.59	—		
Hypercholesterolemia	1.75	0.75–2.24	0.31	—		
Family history for stroke	0.99	0.73–1.76	0.19	—		
History for TIA	1.07	0.95–1.48	0.21	—		
Pre-stroke treatment	0.96	0.74–1.54	0.09	—		
Acute treatment	0.53	0.45–0.60	<0.001	0.46	0.38-0.52	<0.001
Glucose (increase per unit)	1.09	0.98–1.19	0.12	—		
CRP (increase per unit)	1.15	1.03–1.22	0.006	1.09	1.01-1.18	0.011
PLT (increase per unit)	1.02	1.00–1.03	0.053	—		
Small-vessel occlusive	0.58	0.30–1.15	0.072	—		
Large-vessel occlusive	0.88	0.53–1.19	0.31			
Cardioembolic	1.78	1.20-3.90	0.72	—		

†including significant factors confirmed in the univariate logistic regression analysis; ‡AR defined by more than 550 ARU; OR, odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; PLT, Platelet; TPA-T: Tissue plasminogen activator-treated; CRP, C-reactive protein; FBG, fasting blood glucose; AR, aspirin-resistant; TIA, Transient ischemic attack; AS, Aspirin sensitive; ARU, aspirin reaction units

microvascular thrombi, resulting in more severe stroke and larger infarct volumes (22), which associated with mortality. Second, AR may induce mortality through inflammatory mechanisms (23). Third, AR was associated with an increased risk of atherothrombotic vascular events in a wide range of cardiovascular patients (16).

Some limitations in this study should be considered. First, one platelet function test was used to assess AR. Additional laboratory tests that detect platelet cyclooxygenase-1 function should be performed to verify the aspirin compliance and aspirin responsiveness. Second, his observational study cannot determine the causal relationship between AR and stroke mortality. Lastly, the overwhelming majority of our sample was Chinese, limiting the generalizability to other ethnicities. Thus, the findings should be interpreted with caution when generalizing to other patients with stroke.

Conclusions

The present study shows that AR was a useful prognostic marker of all-cause or CVD mortality in Chinese patients with AIS, independent of established conventional risk factors. There is a clear need for future studies to thoroughly evaluate individual determinants of laboratory aspirin resistance, predictive value of the various laboratory methods, and possible solutions for individual patients.

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