Research Article

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Elevated ESRS, serum FIB, Hcy and stroke history were independent risk factors to PAIS

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Abstract: Background: The aim of this study was to investigate the diagnostic performance of serum homocysteine (Hcy) and Essen stroke risk score (ESRS) in prediction of progressing acute ischemic stroke (PAIS).

Methods One hundred and thirty two acute ischemic stroke (AIS) patients were retrospectively recruited from Daping Hospital, Third Military Medical University from February 2016 to January 2018. The 132 AIS patients were divided into PAIS and non-progressing AIS (NPAIS) groups according to the definition of PAIS. The clinical characteristics, serum Hcy concentration, and ESRS were compared between the PAIS and NPAIS groups. The independent risk factors for PAIS were evaluated by logistic regression analysis. The prediction sensitivity, specificity and area under the ROC curve (AUC) of serum Hcy and ESRS for PAIS were calculated using STATA11.0 software.

Results: The elevated ESRS (OR=1.82, $p<0.05$), serum fibrinogen (FIB) (OR=1.18, $p<0.05$), Hcy (OR=1.21, $p<0.05$) and personal stroke history (OR=1.74, $p<0.05$) were independent risk factors for PAIS. The serum Hcy of the PAIS and NPAIS groups were 24.59 ± 9.24 ($\mu\text{mol/L}$) and 18.20 ± 8.29 ($\mu\text{mol/L}$) respectively with a statistical significance of $p<0.05$. The ESRS were 3.43 ± 1.09 and 2.60 ± 0.92 for the PAIS and NPAIS groups respectively, with a significance of $p<0.05$. The prediction sensitivity, specificity and AUC were 76.24%, 67.74% and 0.73 (95%CI:0.63-0.83), respectively, for serum Hcy. For ESRS, the prediction sensitivity, specificity and AUC were 69.99%, 64.52% and 0.74 (95%CI:0.63-0.84) respectively. Correlation between serum Hcy and ESRS was evaluated by a Pearson correlation test. Significant positive

correlation between serum Hcy and ESRS was found in PAIS ($r=0.54$, $p<0.05$), and NPAIS patients ($r=0.78$, $p<0.01$).

Conclusion: Patients with elevated ESRS, serum FIB, Hcy and stroke history had an elevated risk of developing PAIS.

Keywords: ischemic stroke; risk factors; homocysteine; ESRS.

Background

Acute ischemic stroke (AIS) with high morbidity, disability and mortality is one of the most diagnosed ischemic cerebrovascular diseases clinically [1]. It has been reported that about 12% - 42% of AIS was finally diagnosed as progressing acute ischemic stroke (PAIS), which is poor for prognosis compared to non-progressing AIS (NPAIS) [2]. It has been reported that patients with PAIS have prolonged hospitalization, more medical expenses, poor prognosis, severe neurological deficits and an elevated risk of death [3, 4]. However, the etiology and pathogenesis of PAIS is not yet completely clear [5, 6]. Therefore, accurate prediction of PAIS from all the AIS patients is difficult. Several previously published studies have analyzed the potential factors relevant to PAIS, but a consensus has not yet been reached. In our present study, we retrospectively included one hundred and thirty two acute ischemic stroke patients and analyzed the independent risk factors relevant to PAIS and discussed their predication performance.

Materials and methods

Patients

Informed consent: Written informed consent was obtained from all patients according to the declaration of Helsinki.

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Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the University's local ethics committee.

One hundred and thirty two AIS patients were retrospectively analyzed in our hospital. The 132 AIS patients were divided into PAIS and NPAIS groups according to the definition of PAIS. The patients' inclusion criteria were as follows: (1) the AIS was diagnosed by brain MRI or CT; (2) more than 18 years of age; and (3) complete data can be drawn from the medical records. The patients' exclusion criteria were: (1) patients of acute cerebral hemorrhage; (2) patients with encephalitis, cerebral venous thrombosis, brain tumor and transient ischemic attack; (3) HIV positive; and (4) dead within 3 days after hospitalization.

Data collection and risk factors analysis

A unique questionnaire including the patient's name, gender, age and potential relevant risk factors such as hypertension, diabetes, serum low-density lipoprotein (LDL), serum fibrinogen (FIB), Body Mass Index (BMI), unstable plaque of carotid artery (UPCA), smoking history, serum homocysteine (Hcy), family stroke history (FSH), personal stroke history (PSH), alcohol consumption history (ACH), coronary atherosclerotic heart disease (CAHD) and Essen stroke risk score (ESRS) for PAIS were used for collecting the clinical data from the included patients. The data were collected by two researchers by reviewing the medical records and asking the patients or patient guardians independently. The data was cross-checked by the two reviewers. When there was a controversy regarding the clinical data, the cases were re-reviewed and the problem was resolved by discussion.

Statistical analysis

The data were analyzed using STATA11.0 statistical software (<http://www.stata.com>), the measurement data were expressed with $\bar{x} \pm s$ and the comparison between groups was made based on the t-test of the sample mean. The enumeration data were expressed with a relative number, and the comparison between groups was made based on the χ^2 test. The related data were based on the Pearson correlation test. The prediction sensitivity and specificity was calculated by the equation of sensitivity=true positive/(true positive+ false negative),

specificity=true negative/(true negative+ false positive). The area under the receiver operating characteristic (ROC) curve was used to evaluate the feasibility of serum Hcy and ESRS as biomarker for PAIS diagnosis. Two tailed $P < 0.05$ was considered statistically significant.

Results

Relevant factors comparison between PAIS and NPAIS

Significant statistical difference of diabetes history ($p=0.03$), serum FIB level ($p=0.006$), UPCA ($p=0.048$), smoking history ($p=0.02$), serum Hcy level ($p=0.0001$), ESRS ($p<0.0001$) and PSH (<0.0001) were found between the PAIS and NPAIS groups, **Table 1**.

Logistic regression analysis

The logistic regression analysis demonstrated that the elevated ESRS ($OR=1.82$, $p<0.05$), serum FIB ($OR=1.18$, $p<0.05$), Hcy ($OR=1.21$, $p<0.05$) and personal stroke history ($OR=1.74$, $p<0.05$) were independent risk factors for PAIS, **Table 2**, **Figure 1**.

Serum Hcy and ESRS between PAIS and NPAIS

The serum Hcy of the PAIS and NPAIS groups was 24.59 ± 9.24 ($\mu\text{mol/L}$) and 18.20 ± 8.29 ($\mu\text{mol/L}$) respectively with statistical difference ($p<0.05$), **Figure 2a**. The ESRS were 3.43 ± 1.09 and 2.60 ± 0.92 for the PAIS and NPAIS groups respectively, with a significance of $p<0.05$, **Figure 2b**.

Figure 1: Forest plot for independent risk factors for PAIS.

Table 1: The clinical factors comparison between the PAIS and NPAIS groups.

Factors	Total(n=132)	PAIS(n=31)	NPAIS(n=101)	t/ χ^2	p
Age(year) [n,(%)]					
mean	64.4±17.2	63.6±12.2	65.7±15.6	0.69	0.49
>64	79(59.8)	19(61.3)	60(59.9)	0.04	0.85
≤64	53(40.2)	12(38.7)	41(40.1)		
Gender[n,(%)]					
Male	72(54.5)	19(61.3)	53(52.5)	0.74	0.39
Female	60(45.5)	12(38.7)	48(47.5)		
Hypertension[n,(%)]					
Positive	101(76.5)	23(74.2)	78(77.2)	0.12	0.72
Negative	31(23.5)	8(25.8)	23(22.8)		
Diabetes[n,(%)]					
Positive	22(16.7)	9(29.0)	13 (12.9)	4.46	0.03
Negative	110(83.3)	22(71.0)	88(81.1)		
LDL(mmol/L)					
mean	3.36±1.42	3.43±1.26	3.24±1.32	0.71	0.48
>3.36	41(31.1)	11(35.5)	30(29.7)	0.37	0.54
≤3.36	91(68.9)	20(64.5)	71(70.3)		
FIB(mmol/L)					
mean	4.12±1.96	4.88±1.87	3.76±1.21	3.92	0.0001
>4.12	41(31.1)	16(51.6)	25(24.8)	7.60	0.006
≤4.12	91(68.9)	15(48.4)	76(75.2)		
BMI(kg·m ⁻³)					
mean	24.2±3.8	24.4±3.4	24.2±3.6	0.27	0.78
>24.2	71(53.8)	15(48.4)	56(55.4)	0.48	0.49
≤24.2	61(46.2)	16(51.6)	45(44.6)		
UPCA[n,(%)]					
Positive	37(28.0)	13(41.9)	24(23.8)	3.88	0.048
Negative	95(72.0)	18(58.1)	77(76.2)		
Smoking[n,(%)]					
Positive	65(49.2)	21(67.7)	44(43.6)	5.54	0.02
Negative	67(50.8)	10(32.3)	57(56.4)		
Hcy(μmol/L)					
mean	21.2±16.9	26.4±15.2	18.6±11.3	3.09	0.003
>21.2	39(29.6)	17(54.8)	22(21.8)	14.92	0.0001
≤21.2	93(70.4)	14(45.2)	79(78.2)		
ESRS					
mean	2.86±1.55	3.52±1.48	2.61±1.12	3.66	0.0004
>2.86	47(35.6)	21(67.7)	26(25.7)	18.25	<0.0001
≤2.86	85(64.4)	10(32.3)	75(74.3)		
FSH [n,(%)]					

Table 1: The clinical factors comparison between the PAIS and NPAIS groups.

Factors	Total(n=132)	PAIS(n=31)	NPAIS(n=101)	t/ χ^2	p
Positive	22(16.7)	4(12.9)	18(17.8)	0.41	0.52
Negative	110(83.3)	27(87.1)	83(82.2)		
PSH[n,(%)]					
Positive	33(25.0)	20(64.5)	13(12.9)	33.74	<0.0001
Negative	99(75.0)	11(35.5)	88(87.1)		
ACH[n,(%)]					
Positive	61(46.2)	14(45.2)	47(46.5)	0.018	0.89
Negative	71(53.8)	17(54.8)	54(53.5)		
CAHD[n,(%)]					
Positive	25(18.9)	6(19.4)	19(18.8)	0.004	0.95
Negative	107(81.1)	25(80.6)	82(81.2)		

LDL= Low-density lipoprotein; FIB= fibrinogen; UPCA=Unstable plaque of carotid artery; FSH=Family stroke history; PSH= Personal stroke history; ACH=Alcohol consumption history; CAHD= Coronary atherosclerotic heart disease;

Table 2: Independent risk factors for PAIS analyzed by logistic regression test.

Risk factors	OR	95% CI of OR	P-value
Diabetes	0.52	0.18-1.66	0.22
FIB	1.18	1.02-3.21	0.02
UPCA	0.72	0.16-1.89	0.31
Smoking	0.66	0.14-1.64	0.19
Hcy	1.21	1.04-2.68	0.01
ESRS	1.82	1.31-2.45	0.01
PSH	1.74	1.41-2.74	0.01

Prediction value of serum Hcy and ESRS for PAIS

The prediction sensitivity, specificity and AUC were 76.24%, 67.74% and 0.73 (95%CI:0.63-0.83) respectively for serum Hcy, **Figure 3a**. For ESRS, the prediction sensitivity, specificity and AUC were 69.99%, 64.52% and 0.74 (95%CI:0.63-0.84) respectively, **Figure 3b**.

Correlation between Hcy and ESRS in PAIS patients

The correlation between serum Hcy and ESRS was evaluated by a Pearson line regression test. Significant positive correlation between serum Hcy and ESRS was found in PAIS ($r=0.54$, $p<0.05$), **Figure 4a**, and NPAIS patients ($r=0.78$, $p<0.01$), **Figure 4b**.

Discussion

Stroke, one of the leading causes of death and long-term disability in human beings, is the most diagnosed cerebrovascular disease [7, 8]. More than one third of patients with ischemic stroke developed early neurological defects, resulting in elevated mortality and disability [9, 10]. The prognosis of these early progressing ischemic stroke patients is poor [11, 12]. However, the mechanism of early progression of the disease is not fully understood. Several previously published studies discuss the risk factors relevant to early progression of ischemic stroke [13], however, the results were inconclusive [5, 14, 15]. Most of the studies believed that hemostatic activation may be an important cause, or contributor, to progressing ischemic stroke [16, 17]. Several studies showed elevated serum Hcy was more often seen in patients with progressing ischemic stroke and was related to the patients' progress. Sometimes, serum Hcy could even be a biomarker for prediction of the prognosis of ischemic patients.

In our present work we retrospectively included 132 ischemic patients, 31 of these patients developed PAIS, with an incidence rate of 23.5%, similar to Qiu's study [18]. In our study, we also found that an elevated ESRS score, serum FIB, Hcy and personal stroke history were independent risk factors for PAIS. Patients with elevated ESRS, serum FIB, Hcy and stroke history had an elevated risk of developing PAIS. ESRS is generally used for clinical stroke recurrence prediction with an easy operation procedure, and recently, several studies have evaluated

Figure 2: The scatter plot of serum homocysteine and ESRS between PAIS and NPAIS (a:serum Hcy; b: ESSEN score).

Figure 3: The ROC curve for serum Hcy and ESSEN score.

Figure 4: Pearson correlation between Hcy and ESRS in PAIS and NPAIS patients(a:PAIS patients; b:NPAIS patients).

its prediction value for AIS progression with conflicting results [16, 19, 20]. Liu and colleges [21] evaluated the predictive value of ESRS for early recurrence and progression of AIS and found that ESRS had no prediction value in this case. However, Shi et al [18] found that ESRS in early PAIS patients was significantly elevated compared to non-progressing patients and the ESRS could be used as a progression maker for AIS patients. In our present study, the ESRS in the PAIS and NPASI groups were 3.43 ± 1.09 and 2.60 ± 0.92 respectively with a significance of $p < 0.05$. The prediction sensitivity, specificity and AUC were 69.99%, 64.52% and 0.74 (95%CI:0.63-0.84) respectively. These results were generally in accordance with Shi's study.

Hcy, which can be recycled into methionine or converted into cysteine with the aid of certain B vitamins, is a non-proteinogenic α -amino acid. Previously published studies have proved that an elevated serum level of Hcy (hyperhomocysteinemia) makes a person more prone to endothelial cell injury, which leads to inflammation in the blood vessels, which in turn may lead to atherogenesis, which can result in ischemic injury. Hyperhomocysteinemia is therefore a possible risk factor for AIS. Hcy is a known normal intermediate of methionine metabolism, however, several studies have demonstrated that hyperhomocysteinemia might be an independent risk factor for cardiovascular disease [22]. Plasma Hcy level is affected by many factors such as genetic, nutritional, physiological and lifestyle. Of these factors, genetic and nutritional factors play a more important role in the development of hyperhomocysteinemia. For instance, deficiencies of certain vitamins such as folate, vitamins B6 and B12 usually cause hyperhomocysteinemia because they participate in the metabolism of Hcy as enzyme cofactors.

It has been proved that elevated serum Hcy can increase the risk of developing cardiovascular disease, such as stroke and coronary atherosclerotic heart disease. Studies also demonstrate that elevated serum Hcy is closely correlated with plasma neopterin [23,24]. Plasma neopterin is related to the presence of multiple complex atherosclerotic plaques in patients with atherosclerosis related diseases [25]. Recent publications have demonstrated that neopterin predicts future cardiovascular risk in subjects with stable angina pectoris [26]. Bjørnstad et al [27] evaluated the association between plasma Hcy and systemic concentrations of neopterin and C-reactive protein among patients with coronary heart disease. They found that plasma Hcy can predict the risk of acute myocardial infarction in subjects with concomitantly elevated plasma neopterin. In our study, we found that the serum Hcy in PAIS

patients was significantly higher than in the NPAS group with the predictive sensitivity, specificity, and AUC of 76.24%, 67.74% and 0.73 (95%CI:0.63-0.83) respectively. Hcy can activate a variety of inflammatory mediators and damage the endothelium through oxidative stress functions, thrombosis and other mechanisms involved in the development of atherosclerosis. It can also produce excitotoxic effects directly to neurons which promotes the progress of ischemic stroke.

Conclusion

PAIS is common in patients with AIS with poor prognosis. Patients with elevated ESRS, serum FIB, serum Hcy and stroke history had more risk of developing PAIS. These patients need more attention and medical treatment. However, the study was retrospective design with a relatively small sample size. Therefore, the statistical power is limited, and the results should be further proved by well designed prospective randomized clinical trials or high quality meta-analysis.

Abbreviations

PAIS: progressing acute ischemic stroke; Hcy: homocysteine; ESRS: Essen stroke risk score ; AIS: acute ischemic stroke; NPAS: non-progressing AIS; AUC: area under the ROC curve; FIB: fibrinogen; OR: odds ratio; LDL: Low-density lipoprotein; BMI: Body Mass Index; UPCA: unstable plaque of carotid artery; FSH: family stroke history; PSH: personal stroke history; ACH: alcohol consumption history; CAHD: coronary atherosclerotic heart disease; ROC: receiver operating characteristic curve;

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Availability of data and materials: Please contact the corresponding author for data requests.

Authors' contributions: Huiyun Li performed the patients' inclusion and collected the data; Yafei Li wrote the manuscript and made the data analysis. All authors have read and approved the final manuscript.

Ethics approval and consent to participate: This study was approved by the Institutional Review Board at Third

Military Medical University Chongqing 400042. Additional informed consent was not required for this retrospective study.

Competing interests: The authors declare that they have no competing interests.

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