Risk Factors and Gender Difference in the Prediction of Ischemic Stroke in China

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Abstract

Introduction: Stroke is a significant contributor to both disability and mortality, imposing a substantial impact on individuals' lives globally. The majority of stroke inpatients exhibited a higher prevalence of ischemic stroke. The aim of this study was to investigate the relationship between homocysteine (Hcy), blood urea nitrogen (BUN), serum creatinine (Scr), carbon dioxide combining power (CO2CP), and ischemic stroke, with a specific focus on potential gender differences. **Materials and Methods:** The present investigation employed a case-control design, wherein all pertinent data was obtained exclusively from the medical records of Fuzhou First People's Hospital in China. The case group consisted of 130 patients who were admitted to the Neurology Department of Fuzhou First People's Hospital for the treatment of ischemic stroke. The control group consisted of 130 hospitalised patients who did not have ischemic stroke and were admitted to the same hospital over the same period. In this study, data pertaining to physical examination, patients' clinical history, and various biochemical indicators including Hcy, BUN, Scr, and CO2CP were documented in the medical records. The examination of craniocerebral imaging was conducted with computerised tomography (CT) or magnetic resonance imaging (MRI). **Results:** Multivariate binary logistic regression showed Hcy, CO_2CP, FBS, SBP had significant association with ischemic stroke ($p<0.05$). The odds for being ischemic stroke was increased with Hcy (adjusted OR=1.280, 95% CI=1.149-1.427, $p<0.001$), FBS (adjusted OR=1.267, 95%CI=1.067-1.503, $p=0.007$), and SBP (adjusted OR=1.033, 95%CI=1.014-1.051, $p=0.001$). The odds of ischemic stroke decreased with CO_2CP (adjusted OR=0.779, 95%CI=0.691-0.878, $p<0.001$). **Conclusion:** Hcy, FBS and SBP were independent and significant risk factors of ischemic stroke and CO_2CP was the protective factor for ischemic stroke in China. There was no gender difference on Hcy, CO_2CP with the incidence for ischemic stroke.

Keyword: association, ischemic stroke, incidence, level, risk factor

Introduction

Stroke is a significant contributor to both disability and mortality rates, imposing a substantial burden on individuals and families worldwide.[1] Globally, the incidence of stroke in 2016 was recorded as 13.7 million. According to the cited source, it was shown that around 87% of stroke patients were diagnosed with ischemic stroke. The regions with the highest incidence rates of ischemic stroke are primarily observed in countries that were formerly part of the Soviet Union, as well as in developing nations. In China, there has been an observed increase in the incidence of ischemic stroke from 484.13 per 100,000 individuals in 2015 to 520.50 per 100,000 individuals in 2019. Furthermore, it has been noted that the incidence of ischemic stroke is higher among males compared to females during the period from 2015 to 2019. Additionally, it is worth mentioning that individuals aged 65 years and older constitute a significant proportion, specifically 68.98%, of the total stroke patients. This information is supported by Wang[2].

Several studies have indicated that there may be a relationship between homocysteine (Hcy),[3] blood urea

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nitrogen (BUN),[4] serum creatinine (Scr),[5] and carbon dioxide combining power (CO2CP)[6] with ischemic stroke. Due to the absence of more effective treatment modalities for stroke, the current focus has shifted towards preventive interventions as the most viable approach. It is imperative to prioritise the enhancement of research efforts pertaining to risk factors associated with ischemic stroke, with the ultimate goal of mitigating both the mortality and morbidity rates associated with this condition. The primary objective of this study was to investigate the potential link between homocysteine (Hcy), blood urea nitrogen (BUN), serum creatinine (Scr), carbon dioxide combining power (CO2CP), and ischemic stroke, with a specific focus on examining any gender differences in their roles as risk factors for ischemic stroke.

Materials and Methods

Study Design and Sample Size

This was a case-control (retrospective) and single centre study, all data was collected from medical records of Fuzhou First People's Hospital in China, which were ranged from January 2017 to June 2023. Case group were 130 hospitalized patients being treated for ischemic stroke in Neurology Department for Fuzhou First People's Hospital. The control group were 130 hospitalized patients without ischemic stroke in this hospital during same period. For this research, physical examination, patients' clinical history, and the tested biochemical indexes such as Hcy, BUN, Scr, CO_2CP were recorded in the medical records. Craniocerebral imaging examination was checked by MRI scan or CT.

Use 3.1.9.7 edition of G*Power software to calculate minimum sample size of this research. Sample size calculation was according to the results of previous references and the pilot study (20 case and 20 control), based on the 17 clinical parameters: homocysteine, blood urea nitrogen, serum creatinine, carbon dioxide combining power, triglycerides(TG), total cholesterol(TC), high density lipoprotein cholesterol(HDL-C), low density lipoprotein cholesterol(LDL-C), fasting blood sugar(FBS), diastolic blood pressure(DBP), systolic blood pressure(SBP), gender, age, diabetes mellitus(DM), hypertension, coronary heart disease(CHD), dyslipidemia. In the calculation, the power was at 80% and the significance level was set as 0.05. According to sample size calculation the minimum sample size required for this research was 84 each group. Considering the incomplete and missing data, a minimum sample size for this research was considered 130 each group, total was 260.

Subject Recruitment

The medical records spanned from January 2017 to June 2023. The case group consisted of hospitalised patients who were undergoing treatment for ischemic stroke in the Neurology Department of Fuzhou First People's Hospital. The inclusion criteria for the case group are as follows: (1) The individuals included in this study were those who satisfied the diagnostic criteria for ischemic stroke. (2) The diagnosis of ischemic stroke was confirmed through the utilisation of cerebral MRI scans or CT scans. (3) Prior to hospitalisation, none of the patients had received any medical therapy for their stroke. (4) The inclusion criteria required participants to be at least 18 years of age. The exclusion criteria for the case group are as follows: (1) Individuals with a prior history of stroke or cerebral infarction sequelae; (2) Individuals with hemorrhagic stroke; (3) Individuals with cerebral tumours; (4) Individuals with a history of major surgery or serious trauma within one month prior to the stroke event; (5) Individuals with nerve function deficits resulting from a previous history of stroke. The control group consisted of hospitalised patients with non-ischemic stroke who received treatment within the same time frame and at the same hospital. The inclusion criteria for the control group are as follows: (1) Individuals who do not have a history of stroke or any prior occurrence of stroke; (2) Participants who are at least 18 years of age or older. The exclusion criteria for the control group are as follows: (1) Individuals with ischemic stroke or hemorrhagic stroke; (2) Individuals with lacunar infarction, sequelae of cerebral infarction, or posterior circulation ischemia; (3) Individuals with a previous history of stroke, lacunar infarction, or posterior circulation ischemia; (4) Individuals with brain tumour, intracranial infection, or other severe craniocerebral diseases; (5) Individuals with similar diseases caused by vascular factors or leading to impaired neurological function; (6) Individuals with severe infection present before the onset of stroke.

Measures

(1) Clinical history: personal characteristics (age, gender), present disease history (DM, hypertension, CHD, dyslipidemia), past disease history (stroke, lacunar infarction, posterior circulation ischemia) and stroke about family history. (2) Physical examinations (DBP, SBP). (3) Biochemical indexes test: TG, TC, HDL-C, LDL-C, FBS, Hcy, BUN, Scr, CO2CP. Sent all samples for blood to the clinical lab of Fuzhou First People's Hospital, and all biochemistry indicator test results were quality controlled. The instruments used for serum analysis was calibrated according to clinical standard. (4) Craniocerebral imaging examination: patients in case and control group were checked by MRI scan or CT to confirm who had ischemic stroke and who didn't.

Statistical Analysis

The period of data collecting spanned from January 2023 to June 2023. To address the issue of missing data, the Series mean approach can be employed to impute the missing values. The data was analysed using the 26th version of IBM SPSS programme. Quantitative variables in a dataset that follows a normal distribution are typically characterised using measures of central tendency, such as the mean, and measures of dispersion, such as the standard deviation. On the other hand, when dealing with non-normally distributed data, it is more appropriate to describe the central tendency using the median and the dispersion using the interquartile range. Qualitative variables can be summarised effectively

by utilising frequencies and percentages. To compare two groups in the data with non-normal distribution or unequal variance, the Mann-Whitney U test can be employed for quantitative variables. The Chi-square test can be utilised to compare two groups in the context of qualitative factors. The study employed binary logistic regression to analyse the relationship between various exposure factors (Hcy, BUN, Scr, CO2CP, TG, TC, HDL-C, LDL-C, FBS, DBP, SBP, DM, hypertension, CHD, dyslipidemia, gender, and age) and the dichotomized outcome variable of ischemic stroke occurrence. Univariate and multivariate binary logistic regression were employed to examine the potential risk variables. A p-value threshold of less than 0.05 was used to determine statistical significance for all variables. The variables that exhibited p-values below 0.05 in the univariate binary logistic regression were selected for further study in the multivariate binary logistic regression using the forward stepwise approach. The variables that were included in the final model were those with a p-value below 0.05. To assess the discriminatory ability of this model, it is necessary to compute the area under the curve (AUC) of the receiver operating characteristic (ROC). To investigate gender differences in ischemic stroke, we conducted a comparative analysis between the case and control groups, separately for females and males. The Mann-Whitney U test was employed for this purpose. The U test was conducted on the data that did not exhibit a normal distribution or equal variance. For the data that followed a normal distribution and had equal variance, a 2-independent samples t-test was employed. The present study employs multivariate binary logistic regression to examine the association between biochemical factors and the occurrence of ischemic stroke in individuals of different genders. A significance level of 0.05 was established for all tests.

Ethical Considerations

This study was approved by Taylor's University Ethics Committee and Fuzhou First People's Hospital Ethics Committee.

Results

A total of 260 participants were included in this research where 130 in case and 130 in control group. Quantitative variables characteristics of this research was shown in Table 1. There had a difference in Hcy levels between case group 12.47 μmol/L (SD 5.3 μmol/L) and control group 9.42 μmol/L (SD 3.89 μmol/L), had a difference in Scr levels for case group 70.00 μmol/L (SD 22.00 μmol/L) compared to control group 61.00 μmol/L (SD 21.25 μmol/L), had a difference in CO_2CP levels for case group 22.30 mmol/L (SD 3.22 mmol/L) compared to control group 24.70 mmol/L (SD 4.85 mmol/L), had a difference in FBS levels for case group 5.50 mmol/L(SD 1.33 mmol/L) compared to control group 5.20 mmol/L (SD 1.24 mmol/L), had a difference in HDL-C levels for case group 1.10 mmol/L (SD 0.30 mmol/L) compared to control group 1.20 mmol/L (SD 0.50 mmol/L), had a difference in SBP levels between case group 144.00 mmHg (SD 30.00 mmHg) and control group 130.00 mmHg (SD 22.00 mmHg), had a difference in DBP levels in case group 84.00 mmHg (SD 15.00 mmHg) and control group 80.00 mmHg (SD 12.00 mmHg), had a difference in Age between case group 67.00 years old (SD 17.00 years old) and control group 62.00 years old (SD 17.00 years old). Cases levels were higher than controls compared to the opposite in CO_2CP and HDL-C, their differences had statistical significance($p<0.05$). The levels of BUN, TC, TG, LDL-C had no difference between case and control group. Qualitative variables characteristics for this study were shown as Table 2. Comparing case with control group, the difference in Gender had statistical significance($P<0.001$). There had 90 (69.2%) males compared with 40 (30.8%) females for case group; males accounted for 35.4% and while females accounted for 64.6% of controls. In case and control group there had a difference in Hypertension ($P<0.001$). In case group, there were 71 (54.6%) ischemic stroke patients with hypertension compared to 59 (45.4%) ischemic stroke patients without hypertension; There had a difference in Diabetes in case and control group ($P<0.05$), diabetes patients with ischemic stroke accounted for 71.1% were more than diabetes patients without, which was accounted for 28.9%. There was no difference for Dyslipidemia in case group and control group. Univariate binary logistic regression analysis indicated the significant risk factors were Hcy, Scr, CO_2CP, FBS, HDL-C, SBP, DBP, hypertension, DM, Age, Gender as shown in Table 3 ($P<0.05$). The statistical significance was set as p-value under 0.05 for all variables. Those variables whose p-values was smaller than 0.05 in univariate binary logistic regression were screened to continue further analysis in multivariate binary logistic regression with the method of forward stepwise. BUN, TC, TG, LDL-C, Dyslipidemia had no difference in the univariate binary logistic regression ($P>0.05$), which were excluded for further analysis. In multivariate binary logistic regression, after the adjustment for age and gender, Hcy, CO_2CP, FBS, SBP had significant association with ischemic stroke as shown in Table 4-5 ($P<0.05$). The risk of being ischemic stroke increased with Hcy (adjusted OR=1.280, 95% CI=1.149-1.427, $p<0.001$), FBS (adjusted OR=1.267, 95%CI=1.067-1.503, $p=0.007$), and SBP (adjusted OR=1.033, 95%CI=1.014-1.051, $p=0.001$). The risk of ischemic stroke decreased with the increase for CO_2CP level (adjusted OR=0.779, 95%CI=0.691-0.878, $p<0.001$). For every unit increased in Hcy, FBS, SBP levels, the odds for being ischemic stroke was increased by 1.280, 1.267, and 1.033, respectively; For every unit increased in CO_2CP levels, the risk for being ischemic stroke was decreased by 0.779. Hcy, CO2CP, FBS, and SBP were the independent influential factors for ischemic stroke ($P<0.05$). Checked collinearity diagnostics for Hcy, CO2CP, FBS, and SBP, results indicated there was no multicollinearity among them. According to multivariate binary logistic regression, Hcy, CO2CP, FBS, and SBP as well as Gender were included in the prediction model, drew the ROC curve (Fig 1) and calculated AUC value. The AUC value for this model was 0.864 (Table 6), which suggested this predicted model had a good discrimination (Table 7).

Characteristics of quantitative variables in case and control group among males and females were shown in Table 8. There was a difference in Hcy, CO_2CP, SBP, hypertension, and DM in case and control group among males and females, respectively. Cases levels were higher than controls in Hcy and SBP compared to the opposite in CO_2CP, their differences had statistical significance($p<0.05$). It had no difference in TC, TG, LDL-C, dyslipidemia levels in case and control group among females and males, respectively. It had no gender difference between Hcy, CO_2CP levels and the incidence of ischemic stroke (Table 9), increased Hcy, CO_2CP levels were both found to have significant association with ischemic stroke in males and females ($p<0.05$), (adjusted OR=1.217, 95%CI=1.073-1.381, p=0.002), (adjusted OR=0.694, 95%CI=0.594-0.811, p<0.001) in males and (adjusted OR=1.273, 95%CI=1.109-1.463, p=0.001), (adjusted OR=0.821, 95%CI=0.702-0.961, p=0.014) in females.

Table 1: Characteristics of quantitative variables: Mann-Whitney U test.

Variables	Group		p-value
	Case (n=130)	Control (n=130)	
Hcy	12.47 (SD 5.30)	9.42 (SD 3.89)	0.000
Scr	70.00 (SD 22.00)	61.00 (SD 21.25)	0.000
BUN	4.35 (SD 1.75)	4.70 (SD 1.55)	0.252
CO2CP	22.30 (SD 3.22)	24.70 (SD 4.85)	0.000
FBS	5.50 (SD 1.33)	5.20 (SD 1.24)	0.005
TC	4.50 (SD 1.12)	4.57 (SD 1.20)	0.890
TG	1.45 (SD 1.08)	1.39 (SD 0.91)	0.219
LDL-C	2.57±0.85	2.46±0.73	0.270
HDL-C	1.10 (SD 0.30)	1.20 (SD 0.50)	0.000
SBP	144.00 (SD 30.00)	130.00 (SD 22.00)	0.000
DBP	84.00 (SD 15.00)	80.00 (SD 12.00)	0.004
Age	67.00±17.00	62.00±17.00	0.002

Table 2: Characteristics of qualitative variables: Chi-Square test.

Variables	Group		p-value
	Case(n=160)	Control(n=160)	
Gender			
Male	90(66.2%)	46(33.8%)	0.000
Female	40(32.3%)	84(67.7%)	
Hypertension			
Yes	71(67.6%)	34(32.4%)	0.000
No	59(38.1%)	96(61.9%)	
DM			
Yes	32(71.1%)	13(28.9%)	0.002
No	98(45.6%)	117(54.4%)	
CHD			
Yes	5(100.0%)	0(0.0%)	0.024
No	125(49.0%)	130(51.0%)	
Dyslipidemia			
Yes	11(47.8%)	12(52.2%)	0.827
No	119(50.2%)	118(49.8%)	

Table 3: Predictors for ischemic stroke in univariate binary logistic regression (n=260).

Predictor	B	SE	Wald	df	p-value	OR(95%CI)
Hcy	0.273	0.046	34.669	1	0.000	1.314 (1.200, 1.439)
Scr	0.033	0.008	16.402	1	0.000	1.034 (1.017, 1.050)
BUN	0.017	0.069	0.060	1	0.806	1.017 (0.888, 1.165)
CO_2CP	-0.237	0.048	24.630	1	0.000	0.789 (0.719, 0.867)
FBS	0.228	0.075	9.209	1	0.002	1.256 (1.084, 1.455)
TC	0.081	0.127	0.407	1	0.524	1.084 (0.846, 1.390)
TG	0.162	0.120	1.812	1	0.178	1.176 (0.929, 1.488)
LDL-C	0.174	0.158	1.217	1	0.270	1.190 (0.873, 1.623)
HDL-C	-1.676	0.468	12.839	1	0.000	0.187 (0.075, 0.468)
SBP	0.036	0.008	22.505	1	0.000	1.037 (1.021, 1.052)
DBP	0.035	0.011	9.211	1	0.002	1.035 (1.012, 1.059)
Age	0.035	0.011	9.216	1	0.002	1.035 (1.012, 1.059)
Gender						
male	1.413	0.264	28.627	1	0.000	4.109 (2.448, 6.895)
female	ref					
Hypertension						
Yes	1.223	0.266	21.112	1	0.000	3.398 (2.017, 5.725)
No	ref					
DM						
Yes	1.078	0.356	9.156	1	0.002	2.939 (1.462, 5.908)
No	ref					
Dyslipidemia						
Yes	-0.095	0.437	0.048	1	0.827	0.909 (0.386, 2.141)
No						

Table 4: Predictors for ischemic stroke in multivariate binary logistic regression with Forward LR method (n=260).

Predictor	B	SE	Wald	df	p-value	OR (95%CI)
Gender	1.206	0.332	13.178	1	0.000	3.340 (1.742, 6.404)
Hcy	0.247	0.055	19.969	1	0.000	1.280 (1.149, 1.427)
CO_2CP	-0.250	0.061	16.790	1	0.000	0.779 (0.691, 0.878)
FBS	0.236	0.087	7.317	1	0.007	1.267 (1.067, 1.503)
SBP	0.032	0.009	11.992	1	0.001	1.033 (1.014, 1.051)

Table 5: Predictors for ischemic stroke in multivariate binary logistic regression with Enter method, Before and After controlled for Gender (n=320).

Variable	OR(95%CI)	p	AOR (95%CI)	p
Hcy	1.338 (1.201, 1.490)	0.000	1.280 (1.149, 1.427)	0.000
CO_2CP	0.801 (0.717, 0.894)	0.000	0.779 (0.691, 0.878)	0.000
FBS	1.278 (1.077, 1.516)	0.005	1.267 (1.067, 1.503)	0.007
SBP	1.033 (1.015, 1.051)	0.000	1.033 (1.014, 1.051)	0.001

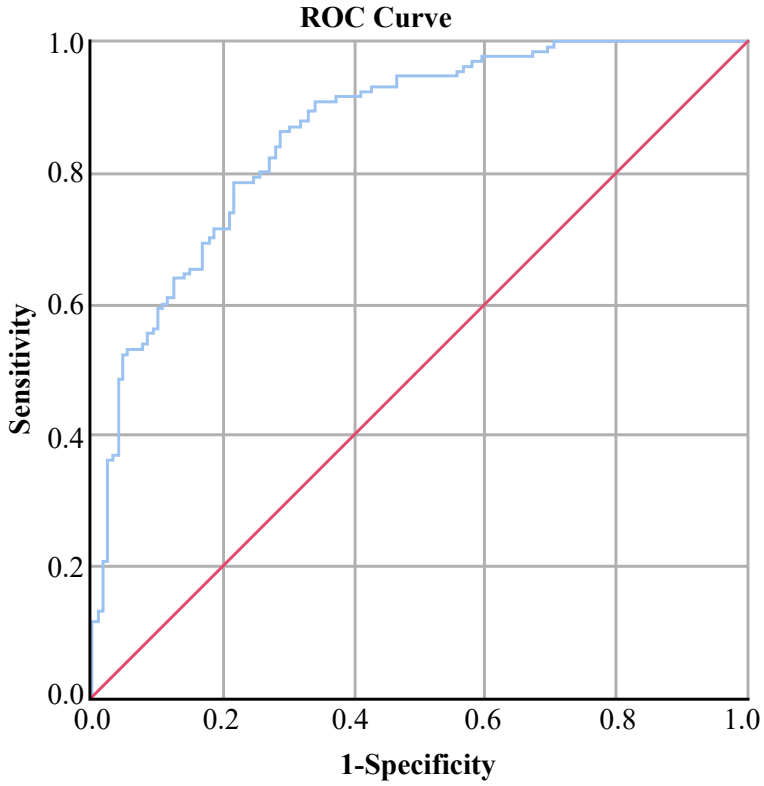

Figure 1. ROC curve

Table 6: AUC value for this study

AUC	p-value	95%CI
0.864	0.000	0.821-0.907

Table 7: Indices for good model fit

Hosmer-Lemeshow Test (p-value)	Classification table (Overall percentage)	Model Summary (-2 Log likelihood)
0.694	77.3%	238.171[a]

Table 8: Characteristics of quantitative variables in male and female group: Mann-Whitney U test

Variables	Group		p-value
	Case	Control	
Hcy			
Male	12.71(5.64)	10.45(4.74)	0.000
Female	12.04(4.59)	8.85(3.73)	0.000
Scr			
Male	75.50(21.50)	74.50(16.00)	0.553
Female	61.50(15.53)	56.00(12.55)	0.037
BUN			
Male	4.45(1.80)	5.15(1.55)	0.005
Female	4.20(1.38)	4.50(1.50)	0.752
CO_2CP			
Male	22.37±2.62	25.12±2.96	0.000
Female	22.65 (3.13)	24.05 (4.55)	0.018
FBS			
Male	5.45(1.22)	5.55(1.25)	0.702
Female	5.86(1.90)	4.94(1.16)	0.001
TC			
Male	4.43(1.03)	4.49(1.47)	0.732
Female	4.88±0.95	0.57±0.92	0.089
TG			
Male	1.36(1.15)	1.23(1.16)	0.505
Female	1.49(0.86)	1.40(0.88)	0.189
LDL-C			
Male	2.51±0.88	2.50±0.77	0.953
Female	2.71±0.76	2.44±0.71	0.057
HDL-C			
Male	1.00(0.30)	1.18(0.34)	0.045
Female	1.10(0.38)	1.30(0.48)	0.078
SBP			
Male	144.00(29.00)	136.00(27.00)	0.020
Female	145.00(35.00)	130.00(20.00)	0.000
DBP			
Male	84.00(15.00)	80.00(13.00)	0.141
Female	82.00(14.00)	80.00(11.00)	0.031
Age			
Male	65.00(17.00)	61.00(20.00)	0.222
Female	70.00(16.00)	62.00(16.00)	0.001
Hypertension			
Male (Yes)	47(75.8%)	15(24.2%)	0.030
Male (No)	43(58.1%)	31(41.9%)	
Female (Yes)	24(55.8%)	19(44.2%)	0.000
Female (No)	16(19.8%)	65(80.2%)	
DM			
Male (Yes)	21(87.5%)	3(12.5%)	0.015
Male (No)	69(61.6%)	43(38.4%)	
Female (Yes)	11(52.4%)	10(47.6%)	0.030
Female (No)	29(28.2%)	74(71.8%)	
CHD			
Male (Yes)	3(100.0%)	0(0.0%)	0.211
Male (No)	87(65.4%)	46(34.6%)	
Female (Yes)	2(100%)	0(0.0%)	0.039
Female (No)	38(31.1%)	84(68.9%)	
Dyslipidemia			
Male (Yes)	7(63.6%)	4(36.4%)	0.853
Male (No)	83(66.4%)	42(33.6%)	
Female (Yes)	4(33.3%)	8(66.7%)	0.933
Female (No)	36(32.1%)	76(67.9%)	

Table 9: Predictors for gender difference in multivariate binary logistic regression in male and female after controlled for age

Variable	Male		Female	
	AOR (95%CI)	p-value	AOR (95%CI)	p-value
Hcy	1.217(1.073, 1.381)	0.002	1.273(1.109, 1.463)	0.001
Scr	1.014(0.993, 1.036)	0.192	1.012(0.983, 1.042)	0.430
BUN	0.922(0.780, 1.090)	0.342	0.823(0.572, 1.183)	0.293
CO_2CP	0.694(0.594, 0.811)	0.000	0.821(0.702, 0.961)	0.014

Discussion

This study examined the association between Hcy, CO2CP, FBS, SBP levels and the incidence of ischemic stroke. Our findings indicate that Hcy, CO2CP, FBS, and SBP levels were significantly associated with the occurrence of ischemic stroke. However, we did not notice a significant association between BUN levels and ischemic stroke. Although there was a significant connection between Scr levels and the risk of ischemic stroke in the univariate analysis, this significance was no longer observed in the multivariate analysis. Homocysteine is an essential amino acid that is not endogenously synthesised by the human body and therefore must be acquired through dietary sources. Prior studies have suggested that homocysteine exerts a significant impact on cardiovascular illness, although there exists limited literature exploring the association between homocysteine levels and cerebrovascular disease. In the present investigation, homocysteine remained statistically significant even after accounting for potential confounding variables. The results indicating a correlation between elevated levels of homocysteine and the occurrence of ischemic stroke were consistent with previous research.[7-9] During the preliminary phase of the research, the reports suggested that there was no correlation between homocysteine levels and ischemic stroke.[10] Subsequently, several studies posited a correlation between fasting homocysteine levels and the occurrence of ischemic stroke.[11] Furthermore, it was shown that ischemic stroke patients exhibited elevated levels of homocysteine in comparison to patients without such condition.[12] These studies did not investigate the fluctuating levels of homocysteine during the acute stage of ischemic stroke among hospitalised patients. The study conducted by Haapaniemi *et al*.[13] assessed the levels of homocysteine throughout the duration of hospitalisation and post-discharge. Specifically, homocysteine levels were measured on the 7th day, 1 month, and 3 months after admission. The findings revealed that homocysteine levels were initially low upon admission, but subsequently increased and remained elevated for a period of 3 months.[13] The study conducted by Shi *et al*.[14] investigated the association between stratified homocysteine levels as quartiles and their relationship with the incidence and mortality rate of ischemic stroke. The findings of the study revealed that those in the highest quartile of homocysteine levels exhibited a significantly greater incidence and death rate of ischemic stroke compared to those in the lowest quartile.[15] In recent years, there has been a growing body of research focusing on the association between levels of homocysteine and ischemic stroke. However, the findings of these studies have been inconsistent with regard to prognosis,[16,17] gender differences, and age.[18,19] The research conducted by Zhong *et al*.[20] shown a correlation between increased levels of homocysteine and a heightened susceptibility to ischemic stroke, with this relationship being more pronounced in females than in males.[20] Conversely, Shi *et al*.[14] highlighted a greater correlation between levels of homocysteine and ischemic stroke in males. The relationship between homocysteine levels and the occurrence of ischemic stroke varied across different age groups.[21] Several studies have examined the association between homocysteine levels and ischemic stroke, with varying conclusions on the influence of age. Some studies have suggested that the relationship between homocysteine levels and the incidence of ischemic stroke is age-dependent, while others have found no significant association between age and the relationship between homocysteine and ischemic stroke.[18] Our study found that elevated levels of homocysteine were identified as an independent risk factor for ischemic stroke. We observed a positive correlation between homocysteine levels and the incidence of ischemic stroke, whereby an increase in homocysteine levels by one unit was associated with a 1.280-fold increase in the incidence of ischemic stroke. Although no significant gender difference was seen, our investigation revealed that both females and males exhibited a link between homocysteine levels and the incidence of ischemic stroke.

In the present investigation, we observed a noteworthy correlation between CO2CP concentration and ischemic stroke. However, it is important to note that this association exhibited an inverse relationship in comparison to other biochemical indicators. The occurrence of ischemic stroke had a negative correlation with elevated levels of CO2CP. Higher concentrations of CO2CP were indicative of a reduced likelihood of experiencing an ischemic stroke. Specifically, for each incremental unit rise in CO2CP concentration, the probability of suffering from an ischemic stroke fell by 0.779. The existing research on the correlation between CO2CP and stroke is currently scarce and significantly constrained. The primary focus of these investigations revolved around the correlation between carbon dioxide cerebral perfusion (CO2CP) levels and the clinical outcomes associated with ischemic stroke. The research conducted by Wang *et al*.[6] demonstrated that decreased levels of CO2CP were associated with an unfavourable prognosis and increased mortality rates among individuals with ischemic stroke (reference). According to the research conducted by Zhang *et al*.[22], it was found that a CO2CP level below 23mmol/L[22] was associated with an unfavourable outcome in individuals suffering from acute ischemic stroke. The findings of our study align with those of previous investigations, collectively demonstrating an inverse correlation between levels of carbon dioxide cerebral perfusion (CO2CP) and the occurrence of ischemic stroke. The use of high levels of fructose, namely in the form of fructose-sweetened beverages (FBS), has been associated with the development of insulin resistance, release of free fatty acids, and dysfunction of the endothelium. These factors, in conjunction with other contributing factors, have been implicated in the increased morbidity of cerebrovascular diseases, including ischemic stroke.[23] According to the study conducted by Hu *et al*.[24], a significant proportion of individuals diagnosed with

ischemic stroke were found to have diabetes mellitus or inadequate glycemic control. The researchers also identified a noteworthy association between elevated fasting blood sugar levels and the risk of developing ischemic stroke. These findings emphasise the importance of implementing improved management strategies and early detection methods for individuals at risk of ischemic stroke.[24] The findings of our study align with those of Hu *et al*.[24]. We have determined that fasting blood sugar (FBS) is significantly associated with ischemic stroke and acts as an independent risk factor for this condition. This conclusion holds true even after accounting for confounding variables in a multivariate binary logistic regression analysis, as the significance of the association remains evident. The occurrence of ischemic stroke demonstrated a positive correlation with fasting blood sugar (FBS) levels. Individuals with diabetes exhibited a higher likelihood of experiencing ischemic stroke in comparison to those without diabetes. Moreover, for each unit rise in FBS concentration, the probability of experiencing ischemic stroke increased by a factor of 1.267. In our investigation, no significant correlation was seen between blood lipids and the occurrence of ischemic stroke. Numerous research have demonstrated a significant association between blood lipids and the susceptibility to cardiovascular illness.[25] Similarly, investigations pertaining to the relationship between blood lipids and ischemic stroke have consistently reported that levels of blood lipids can influence the chance of experiencing an ischemic stroke.[26,27]

Hypertension has the potential to induce ischemic degeneration in the cerebral blood vessels, thereby facilitating the progression of cerebral atherosclerosis. This can lead to the thickening of the walls of cerebral blood vessels, narrowing of the lumen, or rupture of plaque due to cerebral thrombosis. In addition, detachment of thrombus can give rise to cerebral artery embolism, ultimately resulting in insufficient cerebral blood supply or ischemic stroke.[28] In our research, we observed a noteworthy correlation between elevated systolic blood pressure (SBP) and the occurrence of ischemic stroke. This link remained significant even after accounting for potential confounding factors in a multivariate analysis. Specifically, for each unit rise in SBP levels, there was a corresponding 1.033-fold increase in the likelihood of experiencing an ischemic stroke. Our findings provide additional evidence supporting the notion that elevated systolic blood pressure (SBP) is an independent risk factor for ischemic stroke. This finding is consistent with the majority of studies that have reported a relationship between blood pressure levels and the occurrence of ischemic stroke.[29,30] However, it should be noted that our results contradict the study conducted by Wallen *et al*.[31], which suggested that higher SBP levels may actually have beneficial effects in terms of reducing the severity of ischemic stroke and improving the discharge rate.[31]

In our investigation on gender differences, we found that there was no discernible disparity between genders in terms of higher levels of Hcy and CO2CP. However, we did observe that these factors were strongly associated with the risk of ischemic stroke among males and females, respectively. The findings of this study contradict the research conducted by Zhong *et al*.[20], which suggested that there is a gender difference in the prognosis of ischemic stroke related to homocysteine levels. Zhong *et al*.[20] found that high levels of homocysteine in females were significantly associated with the prognosis of ischemic stroke, whereas this link was not observed in males.[20] The findings of this study diverge from our own research on stroke, as they do not pertain to the gender-based disparity in the occurrence of ischemic stroke. Further research is required to substantiate the link between these variables in relation to gender differences.

Like any other scientific investigation, this study has several limitations. (1) Due to the retrospective nature of this research, it is susceptible to selection bias. (2) Our study had some missing data, which were addressed by utilising the series mean method for data imputation. It is important to note that this approach may have a slight impact on the study results. (3) The control group consisted of hospitalised patients without ischemic stroke, rather than relatively healthy individuals undergoing physical examinations or outpatients. This selection criterion may introduce confounding factors, as hospitalised patients may have additional comorbidities. Consequently, small differences between the case and control groups may not be adequately detected. (4) There is a scarcity of literature available for reference and comparison regarding CO2CP and BUN. (5) The number of patients with coronary heart disease (CHD) was limited, and the control group lacked individuals with CHD. Consequently, the association between CHD and ischemic stroke could not be effectively examined. In the investigation of gender differences, the sample size was deemed insufficient for detecting any significant disparities between genders. In this study, there was a lack of investigation of other variables, such as body mass index, which is known to have an impact on the occurrence of ischemic stroke. Due to the immobility of certain patients in the experimental group, the measurement of height and weight for all participants was not feasible, resulting in a dearth of data. Additionally, the information pertaining to the smoking habits of patients was insufficiently detailed for the purposes of comparison and subsequent analysis. Furthermore, the biochemical indicators were only assessed once upon admission and were not subject to subsequent serial dynamic measurements during the initial phases of ischemic stroke. Conducting many measurements at various time intervals can be advantageous in enhancing comprehension of the precise relationship between them.

Conclusion

The present investigation observed a strong association between elevated levels of homocysteine (Hcy), carboxyethyl-lysine (CO2CP), fasting blood sugar (FBS), and systolic blood pressure (SBP) and the occurrence of

ischemic stroke. Homocysteine (Hcy), fasting blood sugar (FBS), and systolic blood pressure (SBP) were identified as statistically significant and autonomous risk factors for ischemic stroke in the Chinese population. Conversely, carbon dioxide cerebral perfusion (CO2CP) was found to exhibit a protective effect against ischemic stroke in China. There was no observed gender disparity in the levels of Hcy and CO2CP, as well as their association with the incidence of ischemic stroke. However, it was shown that elevated levels of Hcy and CO2CP were both associated with an increased risk of ischemic stroke in both males and females. The implementation of targeted interventions and preventative measures among high-risk populations has the potential to decrease the incidence of morbidity associated with this particular disease. It is imperative to conduct a comprehensive nationwide screening of risk factors for ischemic stroke among middle-aged and older individuals, while concurrently implementing intervention research.

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