Homocysteine and Cholesterol: interaction and impact on outcome of ischemic stroke

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Abstract: **Objective and Aim**: To determine the functional outcome in a cohort of patients with ischemic stroke, focusing on homocysteine (hcy) as well as the components of lipid profile and also to elucidate the relationship between hcy with other biochemical parameters. Material and Method: From the patient database of the First Affiliated Hospital of Zhengzhou University, data of total 623 patients were collected. The reports of only ischemic stroke patients were taken into consideration. Multivariate analysis was performed by logistic regression model. The predictor variables were age, sex, vascular risk factors, and other variables associated with outcome (P<0.1) in univariate analyses. **Results and Conclusion**: Average age of patients was 59.35 ±12.90 years, 67.2% being male. Total of 468 (87.3%) patients were found to have hyperhomocysteinemia (hhcy). Average hcy level was found to be 19.2±11.2mmol/l. Similarly 158 (29.5%) were found to have hypercholesterolemia (hTC) while 336 (62.7%) were found to have hyperlipidemia. 105 (19.6%) patients had history of stroke. MRS <3 at 6 months was defined as good stroke outcome. The univariate analysis showed that hhcy, hTC, and hyperlipidemia were statistically significantly correlated with the outcome of stroke (P≤0.1). Low density lipids (Ldl) and Hcy were significantly associated with each other P≤0.05 (P= 0.039, C.I. 1.080～19.677). Similar was the case of TC and Hcy at 10 mmol/l. Interestingly, we found the synergistic effect between hcy and ldl, as well as hcy and TC towards the prognosis of stroke. The relative excess risk of interaction (RERI), attributable proportion due to interaction (AP), and synergy index (SI) of hcy and ldl as 1.827, 39.62%, and 2.024 as well as 0.209, 26.03%, 1.092 respectively. Conclusion- Hhcy, hyperlipidemia, hTC, high blood glucose (diabetes) are significantly correlated with the outcome of stroke. There is a significant intercorrelation of hhcy, TC and hyperlipidemia and positive synergism is observed among hcy and TC as well as hcy and ldl.

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Introduction:

Stroke is a leading cause of death and disability in China. Identification of modifiable risk factors may lead to more effective primary and secondary prevention of stroke related causes. Homocysteine is one of the important risk factors for cardiovascular disease. The concept of adverse effect of hhcy in the course of stroke is not new now but its association with outcome of stroke and correlation with other modifiable factors have less well studied and result has not been uniform and has been controversial. Several researchers have successfully established that hyperhomocysteinemia is correlated with stroke, but very few researches could throw light on the relation of hyperhomocysteinemia and the functional outcome of stroke.[1] It is puzzling that epidemiological studies have not found a clear association between cholesterol levels and ischemic stroke risk[2-5] while randomized intervention trials have found that cholesterol lowering with statins reduces the risk of ischemic stroke. [6, 7] During this research assuming that if an association of hcy with cholesterol was present, we wished also to examine whether this association was stronger than that of each single factor with outcome following stroke. Smoking relating with increment of homocysteine level has been established. This can be taken as an example of interrelation between some modifiable factors. [8] Kalantar-Zadeh et al. demonstrated negative but not significant correlation between homocysteine and cholesterol. [9] The aim of this study was to assess the association of homocysteine as well as the other risk factors with the functional outcome of stroke. We aimed to depict 6-month functional outcome (prognosis) in adults after ischemic stroke. We also tried to find out the possible interrelation among hcy and other different risk factors. If the relation existed, then our aim was to find out the type of interrelation. Furthermore, we sought to study in our large cohort whether these associations are independent of stroke etiology and other known prognosticators.

2. **Study Design**:

Material and Method: This was an observational of study conducted at the department of Neurology, First Affiliated Hospital of Zhengzhou University, and

was approved by the relevant local authorities and the Ethics committee. Study protocol was in accordance with the declaration of Helsinki. The data of the patient were collected from the database provided by the department of Neurology. Among the data of total 623 patients which were collected, 536 patients were found eligible for study. The Stroke diagnosis was Stroke diagnostic criteria of World Health Organization 1976 was adapted as the basis of stroke diagnosis. [10] Cerebral hemorrhage was excluded by available CT/MRI reports. Patients with other diseases like the report of hematological diseases or renal failure or hepatic failure or patients with dependence caused by any reason before onset of stroke were excluded. The ischemic stroke patients' reports were only taken into consideration. The patient registry form included gender, age, National Institute of Health Stroke Scale (NIHSS) score after admission, hypertension, diabetes, lipid profile: total serum cholesterol (TC), low density lipid (ldl), triglyceride (TG), other blood biochemistry report was noted, history of atrial fibrillation (AF) and coronary heart disease (CHD), Myocardial Infarction (MI), Transient Ischemic Attack (TIA) and smoking, previous stroke history, fasting blood glucose, blood pressure on admission, the level of homocysteine and other laboratory reports, and the treatment reports. Plasma homocysteine level, along with blood lipid level, blood cholesterol, triglyceride etc. measured at second day of admission. The cutoff level of homocysteine, total cholesterol, low density lipid, high density lipid, and triglyceride were set as 10μmol/l, 5.1μmol/l, 2.6μmol/l, 2.21μmol/l, 1.7μmol/l respectively. [11] Patients were followed-up to document recurrent stroke and medication at 6 months. The functional outcome was measured as Modified Rankin Scale (MRS) which was measured in 6 months for which cutoff value of MRS was assigned as 3. [12] Death was included in the bad outcome. Stroke etiologies was assigned by stroke physicians according to the Trial of Org in Acute Stroke Treatment (TOAST) criteria.[13]

Statistical Analysis: Univariate analysis was used to identify factors associated with the outcome of stroke. The factors were grouped as dependent group (having MRS value ≥3) or independent group (MRS value <3). The outcome of stroke was based on MRS score (good outcome indicated when MRS<3, bad outcome when MRS≥3). The association was considered significant with P<0.1. Multivariate logistic regression analysis was used to identify confounding factors and to know the strength of interrelation between different risk factors. Factors that contributed to the recurrence in the initial univariate analyses at P ＜0.1 were included in the multivariate model. In the final multivariate analyses, statistically significance was assumed when P＜0.05. The Statistic Package for Social Science version 17(SPSS inc., Chicago) was used for statistical analysis.

3. **Results**:

Data of total 623 patients were collected. Among them 536 patients were found eligible for study after excluding the records of those patients with missing follow up records or missing blood biochemical profiles.

Among 536 patients, 306 were males. Prevalence of Hcy was seen as the highest in our stroke cohorts (87.3%).Hypertension was seen as another common factor among our cohorts (58%) (among which those on antihypertensive were also included.) Other important factors like atrial fibrillation, TIA history were not found in high prevalence in our cohorts.

3.1. The Demographic and Clinical characteristics of patients presented in the Table 1 & 2.

Table 1: Demographic and Clinical Characteristics of patients

Variables	N	%
SEX（MALE）	360	67.2
HCY	468	87.3
LDL	336	62.7
TC	158	29.5
TG	213	39.7
HDL	522	97.4
HTN	312	58.2
DM	148	27.6
AF	20	3.7
MI	16	3
History of TIA	32	6
History of Stroke	105	19.6
Smoking	185	34.5
Antiplatelet	465	86.8
Anticoagulants	21	3.9
Chinese Medicine	463	86.4
Rehabilitation	114	21.3
MRS≥3	142	26.5

DM-Diabetes Mellitus, HTN-Hypertension, HDL-High Density Lipid, LDL-Low Density Lipid

Table 2. Clinical Characteristics of patients

Variables	Minimal	Maximal	Mean±SD	Median
Age	22	92	59.35±12.90	
NIHSS (IQR)	1	36		6
Blood Glucose (mmol/L)	3	20.64	6.09±2.55	

3.2. Results of baseline characteristics of dependent and independent group: Patients were divided into two groups, the dependent group and

independent group (based on the MRS scoring as indicated above) and the results showed dependent patient comprising of 142 patients, were slightly of older age than the independent group. NIHSS at the time of admission were higher in the dependent group than that of independent. The details are presented as in table 3.

We used univariate analysis and found the relation of different factors with outcome of stroke at P<0.1. Interestingly, hhcy (P 0.039) was statistically significantly related with stroke outcome. So was the case with hypercholesterolemia (P=0.05), hyperlipidemia (P=0.000), diabetes (P=0.000), history of stroke (P=0.000). The detail is presented in the table 4.

Table 3. Baseline characteristics of patients

Variables	Independent (n=394)	Dependent (n=142)	Statistical value	P value
Age (years)	57.88±12.58	63.42±13.00	-4.461	0.000 *
At the Admission NIHSS	4.27±4.84	10.75±8.51	-10.984	0.000 *
FBG at the time of Admisssion（mmol/L）	5.91±2.56	6.60±2.46	-2.787	0.006 *

Table 3- Results of baseline characteristics. (Data expressed as Mean±SD, * P significant at P= ≤0.05), NIHSS- National Institute of Health Stroke Scale, FBG- Fasting Blood Glucose Level

Table 4. Univariate Logistic Regression Analysis

Variables	Independent (n=394)	Dependent (n=142)	Statistical value	P value
HCY	337	131	4.256	0.039*
LDL	228	108	14.763	0.000 *
TC	103	55	7.959	0.005 *
TG	162	51	1.179	0.278
HDL	386	136	1.977	0.160
HTN	214	98	9.271	0.002 *
DM	91	57	15.171	0.000 *
FA	10	10	5.895	0.015 *
MI	12	4	0.019	0.891
History of TIA	20	12	2.117	0.146
History of stroke	75	42	11.080	0.001 *
Smoking	140	45	0.682	0.409
Sex（Male）	263	97	0.115	0.735
Antiplatelet	346	119	1.464	0.226
Anticoaglants	14	7	0.525	0.469
Chinese medicine	341	122	0.036	0.851
Rehabilitation	81	33	0.448	0.503

Table 4 show the results of significance of variables to the outcome of stroke. (* Significant P value at P≤0.1) (HCY- homocysteine, HDL-High density Lipid, TC- triglyceride, LDL- Low density Lipid, HTN- Hypertension,DM- diabetes Mellitus, FA- Fatty Acids, MI- Myocardial Infarction, TIA- Transient Ischemic Attack)

3.3 To find out the interrelation of different available factors and to find the strength of relation of these factors with the outcome of stroke, we chose to do multivariate analysis. We selected statistically significant factors from univariate analysis and proceeded with them in the multivariate analysis, with P≤0.05. The forward regression model was applied. We found strength of association of hyperlipidemia and hhcy as weak (P=0.039). while a strong association was found with hhcy and hypercholesterolemia (P=0.026). Age was significantly interrelated and it was also found to be significantly associated with the outcome of stroke. Similarly diabetes was found to be statistically significantly related too.

The cutoff value of hcy was 10μmol/l , and hyperlpidemia named as higher than cutoff value of 2.6μmol/l The detail is as presented in table 5 and 6.

Table 5. Results of Multi Variate Analysis

Variable	Sig	OR	5.0% C.I.for EXP(B)
Only hyperlipidemia	0.386	2.074	0.398～10.795
Onlyhhcy	0.477	1.710	0.398～7.512
Hyperlipidemia and hhcy	0.039 *	4.611	1.080～19.677
Age	0.000 *	1.036	1.016～1.056
HTN	0.054*	1.587	0.992～2.537
Diabetes	0.041 *	1.860	1.026～3.369
AF	0.354	1.749	0.536～5.705
BG	0.951	1.003	0.906～1.110
Severity	0.000 *	1.168	1.118～1.219

(AF- Atrial Fibrillation, BG- Blood Glucose, P≤0.05)

Table 6 Results in Logistic Multi Variable Analysis

Variable	Sig.	OR	95.0% C.I.for EXP(B)	
Only hypercholesterolemia	0.397	1.902	0.430	8.420
Only hhcy	0.113	2.357	0.817	6.801
Hypercholeteolemia and hhcy	0.026*	3.468	1.161	10.360
Age	0.001*	1.032	1.012	1.052
Hypertension	0.115	1.460	0.912	2.335
Diabetes	0.184	1.480	0.830	2.638
AF	0.384	1.675	0.525	5.348
HistoryofStroke	0.080 *	1.616	0.943	2.770
BG	0.555	1.031	0.933	1.139
Severity	0.000 *	1.161	1.113	1.211

Result of intercorrelation of different variables and outcome of stroke (* Significant P value, P≤0.05)

3.4 Measures of biological interaction were calculated to find out the strength of interaction, and the result showed a strong interaction. We found hcy and ldl were strongly synergistically interrelated and OR value was 4.611, value of Relative Excess Risk due to Interaction (RERI) was found to be 1.827. Similarly OR of total cholesterol and hcy was found to 3.468, and RERI was 0.209 which shows the weak interaction between hcy and total cholesterol. Detail of which is presented in table 6 and table 7

Table 6 Synergistic Effect of LDL and hhcy on prognosis of stroke

Synergistic Effect of LDL and Hyperhomocystemia on Prognosis of Stroke							
LDL	HCY	Dependent	Independent	OR value	RERI	AP	S
-	-	10	54	1			
+	-	8	36	2.074			
-	+	24	112	1.71			
+	+	100	192	4.611	1.827	39.62%	2.024

Table7 Synergistic Effect of TC and Hyperhomocystemia on Prognosis of Stroke

Synergistic Effect of TC and Hyperhomocystemia on Prognosis of Stroke							
TC	HCY	Dependent	Independent	OR value	RERI	AP	S
-	-	5	38	1			
+	-	6	19	1.902			
-	+	79	253	2.357			
+	+	52	84	3.468	0.209	26.03%	1.092

4. **Discussion**:

We have focused our research towards possible association of hcy with the outcome of stroke in 6 months and thus we have tried to find the predictive value for it regarding the stroke outcome. We have also tried to find the possible interaction of hcy with other risk factors, and the type of effect they will exert. Most of the studies done regarding the prognosis of ischemic stroke patients were primarily focused on new stroke incidence and mortality. To the best of our knowledge this study is among the very few which endeavors the type of association of hcy with other risk factors and their combined predictive value in stroke outcome. We were fully aware of the dynamic changes of lipids in stroke patients[14]. So arrangement for the taking blood biochemistry profile was within 48 hours. The result of our study shows that hhcy is significantly (P<0.1) associated with bad outcome of stroke in 6 months. Our study shows consistency with the study of Kado et al. His study found that elevated plasma hcy level may also be related with increased physical function decline [15] and Ribo M et al found that patients who experienced early neurological worsening tend to have higher homocysteine levels.[16] The strength of association observed in our study was loose (P 0.039), the reason of which may be a small number of cohorts included, but there were 87% patients with hhcy in our cohorts which is very high in terms of prevalence in our patients cohorts. With relation to cholesterol; however, it is puzzling that epidemiological studies have not found a clear association between cholesterol levels and ischemic stroke risk[17-20] while randomized intervention trials have found that cholesterol lowering with statins reduces the risk of ischemic stroke [21] In retrospective study conducted recently concluded that functional outcome in elderly survivors of acute ischemic stroke undergoing rehabilitation is slightly more favorable in hypercholesterolemic patients, independently of a large number of prognostic factors.[22] However, some other studies were unable to show such a favorable effect of high total cholesterol (HTC) on stroke outcomes.[23] Similar results were found after analyzing exclusively ischemic stroke cases.[24] Our result also shows the association of total hyper cholesterolemia (above 5.1mmol/l) with the unfavorable stroke prognosis. Although the link between cholesterol and stroke is controversial, the balance of evidence suggests higher cholesterol is associated with an increased risk of atherothrombotic stroke but a reduced risk of intracerebral hemorrhage. Selecting statistically significant factors from the univariate analysis to multivariate analysis, our study showed that when total cholesterol alone was calculated, it appeared insignificant, while when calculated with hcy, we found significant association of cholesterol with hcy. Through this we assume that many studies which found that hypercholesterolemia was a prognostic factor for good functional outcome, they have failed to include hcy in their study. Hence it is quite possible; hcy may have acted as a confounding factor influencing the result. It has been speculated that lower serum cholesterol in relatively elderly patients may simply reflect poor nutritional status, which could predispose to a poor outcome after stroke.[25] They might not have possibly taken into account the nutritional status of patients. Taking these and our results into consideration, we would beg to differ from those claiming hypocholesterolemia as a good prognostic factor.

Hyperlipidemia as a causal factor for atherosclerosis development is already very well established and once the controversial issue is now a history. There are some studies that speak for relation of lipids with the risk of stroke. Levels of total serum lipids are known to be negative acute-phase reactants, and [26,27] hence decrease after stroke. A meta-analysis of 90,000 patients in previous randomized statin trials showed that the reduction in the risk of stroke was related to the extent to which LDL cholesterol levels were lowered [28]. Low-density lipoprotein cholesterol (LDL-C) and non–high-density lipoprotein cholesterol levels were associated with a paradoxical reduction in risk of stroke in NOMAS study, but level analysis done was exploratory, and for this it cannot act as solid body of evidence and when those taking cholesterol modifying medications were excluded, paradoxical relation was no longer observed, and trend towards increased risk of ischemic stroke with increased lipid level (more than 130mg/dl.) [29] A separate study done by Wei Li et al. states that there was no significant relationship between LDL-C levels and 3-month outcome of stroke.[30] We found that lipid was statistically significantly related with the outcome of stroke and it was observed as strong (P 0.00) which agrees to the result and conclusion drawn from studies.

Our study showed an interesting fact that TG had no significant difference in stroke outcome in 6 months in our patients (P 0.278). The result of study by Wei Li et al reflects some resemblance with us[30]. In their study TG was not significantly associated with the stroke outcome in 3 months. Some study does not agree with us. They found TG to be associated with the outcome[31] but information on weight and waist circumference was not collected in this study whereas TG also correlates strongly with body mass index and waist circumference and in both sexes, this relationship is closer than that with cholesterol. [32] Although one small study found no relationship between body mass index and outcome following stroke [33], such variables require investigation as possible predictors of stroke outcome in future studies. Besides, we also tried to find out the type of association of hcy with different factors. Among that, we found hcy was significantly associated with

cholesterol. Same way, hcy was found to be associated with ldl. Interesting result was that the association was found to be synergistic.

There have been many studies conducted towards understanding the type of combination between hcy and lipoproteins or cholesterol. In vitro studies have shown that Hcy enhances the binding of Lp(a) to fibrin by altering fibrinolysis.[34] Nevertheless, only a few studies have evaluated the clinical effect of the biological interaction between Lp(a) and Hcy, finding that the associated risk was greater than the 2 risks independently. However, this synergistic effect was only seen in women[35,36] and no significant interaction was seen in men.[37,38] Hcy, a reducing agent, is capable of modifying the structure and function of Lp(a) in human plasma. Both molecules influence haemostatic function either by altering the endothelium or platelet function or by favoring a thrombotic-prone condition. Possible interaction of cholesterol and homocysteine A lab study done on a APOE knockout mice, suggested that hhcy and hypercholesterolemia, alone or in combination, produce endothelial dysfunction and increased susceptibility to thrombosis in Apoe-deficient mice[39] The combination of high Lp(a) and Hcy levels synergistically increases the likelihood of developing CAD in male patients [40] but their study also found the association to be synergistic interaction in male population, probably due to the special characteristics of our ethnic group, which has the highest prevalence of the MTHFR mutation. The results of these several studies favor our study, in which we have found to be the positively interrelated and the relation to be synergistic between hhcy and hyperlipidemia. Several potential mechanisms for the observed relationship between hhcy and altered lipid metabolism have been proposed, including transcriptional up regulation of cholesterol synthesis attributable to effects of homocysteine on hepatic endoplasmic reticulum (ER) stress and activation of sterol regulatory binding proteins (SREBP), hhcy also enhances LDL uptake. This may be playing the role in the athermatous formation oxidative stress and vascular injury.

Conclusion:

In this study early predictors of functional outcome after stroke were identified. The possible types of association between those factors were also explored. The major finding of this study was that high homocysteine level, high cholesterol, and high lipid each predict bad stroke outcome in follow-up of 6 months. The interrelation between homocysteine and cholesterol is of synergistic type which means the effect of two factors combined is much higher than the effect of factors in single. So bringing down to the lower level of these factors would certainly play role in good outcome of stroke can facilitate its good recovery. However, the interrelation between these different factors cannot be confirmed through such a retrospective observational study. So a prospective follow-up study at large base with case control method is needed.

Conflict of Interest: None to disclose

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