Original Research Article

Study of cholesterol levels in patients with ischaemic stroke and their outcome

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Abstract

Background: Stroke is a major health problem in India. Stroke burden has been rising in India as compared to the developed countries. Recent studies have shown that high serum cholesterol is associated with clinically less severe ischaemic strokes and better outcome.

Aim: The primary objective of the study was to compare the outcome of patients with ischaemic stroke to their cholesterol levels and to correlate the cholesterol levels to the stroke outcome.

Materials and methods: This hospital based prospective follow-up study was conducted in 140 patients admitted with ischaemic stroke in the medical wards of Medical College hospital, Trivandrum. Patients were divided into 2 groups based on cholesterol levels as <160 mg/dl and >160 mg/dl. Their clinical severity at presentation was calculated by Scandinavian stroke scale (0=worst, 58=best) and outcome of these patients at the end of 1 year was measured by Modified Rankin scale (0=best, 6=worst).Serum cholesterol was measured using enzymatic method.

Results: Mean age of 140 patients of at presentation was 63.4±11.9 years of which 53.5% (n=75) males, the mean Scandinavian stroke scale (SSS) being 28.3±12.5. The mean SSS score of high cholesterol group was 39.6 whereas 17 in the low cholesterol group ($p<0.001$). Similarly, the size of infarct in CT brain, outcome variables of modified Rankin scale and mortality were statistically significant between these groups ($p<0.001$). Bivariate correlation analysis showed that increased serum cholesterol level is associated with increased SSS score (positive correlation) with high statistical significance ($p<0.001$). Logistic regression adjustedwith other risk factors showed high cholesterol levels are associated with better outcome and decreased mortality, which is supported by Kaplan-Meier survival analysis.

Conclusion: Hypercholesterolemia is associated with clinically minor strokes and better outcome, whereas major strokes are commonly seen in patients in the low cholesterol group. Hence post stroke outcome is inversely related to serum cholesterol levels in ischaemic stroke patients.

Key words

Cholesterol level, Ischaemic stroke, Outcome.

Introduction

Stroke is defined according to WHO as rapidly developing clinical signs of focal disturbance of cerebral functions with symptoms lasting for 24hours or longer or leading to death, with no apparent cause other than vascular origin. Stroke is the second most common cause of mortality worldwide, causing 6.7 million deaths in 2012, only behind ischaemic heart disease. Stroke is the most common cause of disability and the third common cause of mortality in the United States and most developed countries.

Developing countries like India are at the risk of increasing prevalence of both communicable and non-communicable diseases. Stroke is one of the common causes of morbidity and mortality in India. The adjusted prevalence rate which was estimated was found to be in stroke range, 84 - 262 per lakh in rural and 334 - 424 per lakh in urban populations. In the recent population based studies, the incidence rate of stroke is 119-145 per lakh population. This is associated with a wide variation in case fatality rates with Kolkata having the highest at 42% [1]. Overall, ischemic strokes contributes to about 80% of all strokes in India and intracranial atherosclerosis tends to be commoner in Indian people [2].

More than the mortality, the disability caused by stroke and the economic burden it causes in a developing country like India is very significant. The World Health Organization (WHO) has estimated that the disability-adjusted life years (DALYs) lost due to stroke, a measure of the burden of disease, will rise from 38 million in 1990 to 61 million in 2020.

Risk factors of stroke have been broadly classified as modifiable and non-modifiable. The non-modifiable risk factors include age, sex, ethnicity/race and family history. Stroke risk varies according to differences in these factors. Modifiable traditional risk factors include hypertension, diabetes, dyslipidaemia, atrial fibrillation, smoking, obesity and carotid artery disease. Novel risk factors include hyperhomocysteinemia and hypercoagulable states.

Among the two major types of strokes, ischaemic strokes contribute to about 80% as already mentioned; and haemorrhagic strokes by 20%. Hypertension is the major risk factor accounting for both the subtypes of strokes, whereas atrial fibrillation, smoking, carotid disease, hypercoagulable states predisposes more to ischaemic stroke than to haemorrhagic stroke.

In case of dyslipidaemia, initially it was thought to be a risk factor for both the subtypes of stroke, later multiple studies proved that the patients with low cholesterol levels are in danger of developing haemorrhagic stroke, rather than dyslipidaemia. Recent studies have shown that even patients with ischaemic stroke having low baseline cholesterol levels has poor outcome and increased mortality among various population groups [3].

In this context this study has been done to compare the outcome of patients with ischaemic stroke based on their cholesterol levels.

Materials and methods

This was a Hospital based Prospective follow-up study done in the Medical wards, Department of Internal Medicine, Medical college hospital, Trivandrum, a tertiary care referral & teaching Hospital. The study was conducted from January

2014 to June 2015 in all patients admitted in medical wards with proven ischaemic stroke.

Exclusion Criteria

- Patients with co-morbidities (CAD,COPD,CKD) prior to admission
- Patients previously on statins (hypolipidemic drugs)
- Patients not willing to sign the consent

The sample size of the population is calculated using the formula

$$N = \frac{3.84 \times P \times Q}{L^2}$$

Where:

P=prevalence of high cholesterol levels compared with low and normal cholesterol levels, which is calculated from the study by Zuliani G, et al. [4]

Q=100-P

L = Relative precision of the estimate

Substituting the values,

N = 70

Considering the study design of two groups, the sample size was fixed as 2×70 = 140

Patients admitted with ischaemic stroke in medical wards, Medical college hospital, Trivandrum, who were satisfying inclusion and exclusion criteria were recruited for the study. Written and informed consent was obtained from each participant. A structured proforma was used for recording information. Detailed history, clinical and neurological examinations were done.

Patients were assessed for clinical severity at the time of their admission to wards using Scandinavian Stroke Scale which uses scoring for individual symptoms and its spectrum. Consciousness, orientation, speech, eye movements, motor power of arm, hand and leg, facial palsy and gait were assessed. The scale is graded from 0 to 58 with 0 being the worst and 58 being the best score.

Relevant investigations like Complete Blood Counts, Liver Function Tests, Renal Function Tests, Fasting Blood Sugar and Serum cholesterol were done. Serum cholesterol was done within 24 hours of admission as a fasting value by enzymatic method. Patients were divided into 2 groups based on their cholesterol levels as <160 mg/dl and >160 mg/dl.

These patients were followed up for 1 year to study the outcome. Outcome of the patient was assessed using modified Rankin scale at the end of 1 year, which has a range of 0 to 6, with 0 indicating no symptoms at all and 6 indicating death.

The collected data were consolidated in MS excel and analysed using appropriate statistical techniques using SPSS Statistical Package for the Social Sciences for Windows (Version 16). Relevant statistical tests were used to interpret the results

Approval of the thesis protocol from the institutional research committee of Government medical college, Thiruvananthapuram was obtained. The study was conducted only after the clearance from institutional ethical committee was attained. Written informed consent was obtained from the person (patient/relative) who was being investigated. Privacy and confidentiality was maintained at every stage of the study.

Results

A total of 140 patients with ischaemic stroke who were admitted in wards of Medical College Hospital were studied. Patients were divided into 2 groups based on their cholesterol levels. The mean age of presentation among the total 140 patients was 63.4 years with S.D. of 11.97. The youngest presentation was at 36 years and the oldest at 90 years. The mean age in high cholesterol group was 64.06 years and in low cholesterol group it was 62.7 years (**Table – 1**).

Apart from atrial fibrillation there was not much of statistically significant difference in the distribution of risk factors among both the groups.

The mean SSS value for 140 patients was 28.3 with S.D. 12.5. The mean in the high cholesterol group was 39.6 with S.D. 6.5, and the mean value in low cholesterol group was 17 with S.D. 3.8 (**Table – 2**).

Table - 1: General characteristics and risk factor profiles of the patients.

VARIABLE	CATEGORY	FREQUENCY			% N=140	CHI-SQUARE	P VALUE
		N=140	CHOL>160 N=70	CHOL<160 N=70			
SEX	MALE	75	36	39	53.6%	0.25	0.611
	FEMALE	65	34	31	46.4%		
DM	YES	78	41	37	55.7%	0.46	0.496
	NO	62	29	33	44.3%		
HYPERTENSION	YES	102	51	51	72.9%	0.00	1
	NO	38	19	19	29.1%		
SMOKING	YES	50	27	23	35.7%	0.49	0.48
	NO	90	43	47	64.3%		
ALCOHOLISM	YES	31	16	15	22.1%	0.04	0.839
	NO	109	54	55	77.9%		
AF	YES	20	6	14	14.3%	3.73	0.05
	NO	120	64	56	85.7%		

Table - 2: Distribution of SSS.

	MEAN	S.D.	95% C.I.	T SCORE	P VALUE
N=140	28.3	12.5			
CHOL>160 (N=70)	39.6	6.5			
CHOL<160 (N=70)	17	3.8	20.81-24.38	25.009	p<0.001

Table - 3: Mortality distribution.

OUTCOMES	GROUPS			95% C.I. (OR)	CHI-SQUARE	P VALUE
	N=140	CHOL>160 N=70	CHOL<160 N=70			
ALIVE	106	68	38	6.5126.1 (28.63)	**34.96**	**p<0.001**
DEATH	34	2	32			

Out of 140 patients in the study, 34 patients (24.28%) expired at the end of the follow up of one year. Only 2 patients (0.02%) expired in the high cholesterol group, whereas 32 patients (45.71%) expired in the low cholesterol group (**Table – 3**).

The outcome of the patients at the end of one year was measured using modified Rankin scale of values 0 to 6. The distributions of these variables among the two groups were studied. Out of the 140 patients, at the end of one year follow up, 106 patients were alive, and nobody had a complete recovery of their deficits, so nobody had values of 0 and 1 at the end of 1year (**Table – 4**).

A bivariate analysis of serum cholesterol levels with SSS value shows a positive correlation with a Pearson correlation value of 0.832 with a statistical significance correlation p<0.001 (**Figure – 1**).

The outcome using modified Rankin scale, 0-3 is taken as favourable outcome and 4 -6 was taken as unfavourable outcome and is designated as the dependent variable. The risk factors were taken as independent variables (**Table – 5**).

The high cholesterol group had 97% survival rate at the end of one year, whereas only 54% in the low cholesterol group (**Figure – 2**).

Table - 4: Outcome was assessed using modified rankin scale.

OUTCOME	GROUPS			CHI-SQUARE	P VALUE
	N=140	CHOL>160 N=70	CHOL<160 N=70		
2	53	51	2	93.83	p<0.001
3	20	13	7		
4	6	2	4		
5	27	2	25		
6	34	2	32		

Figure - 1: Bivariate correlation of serum cholesterol with SSS values.

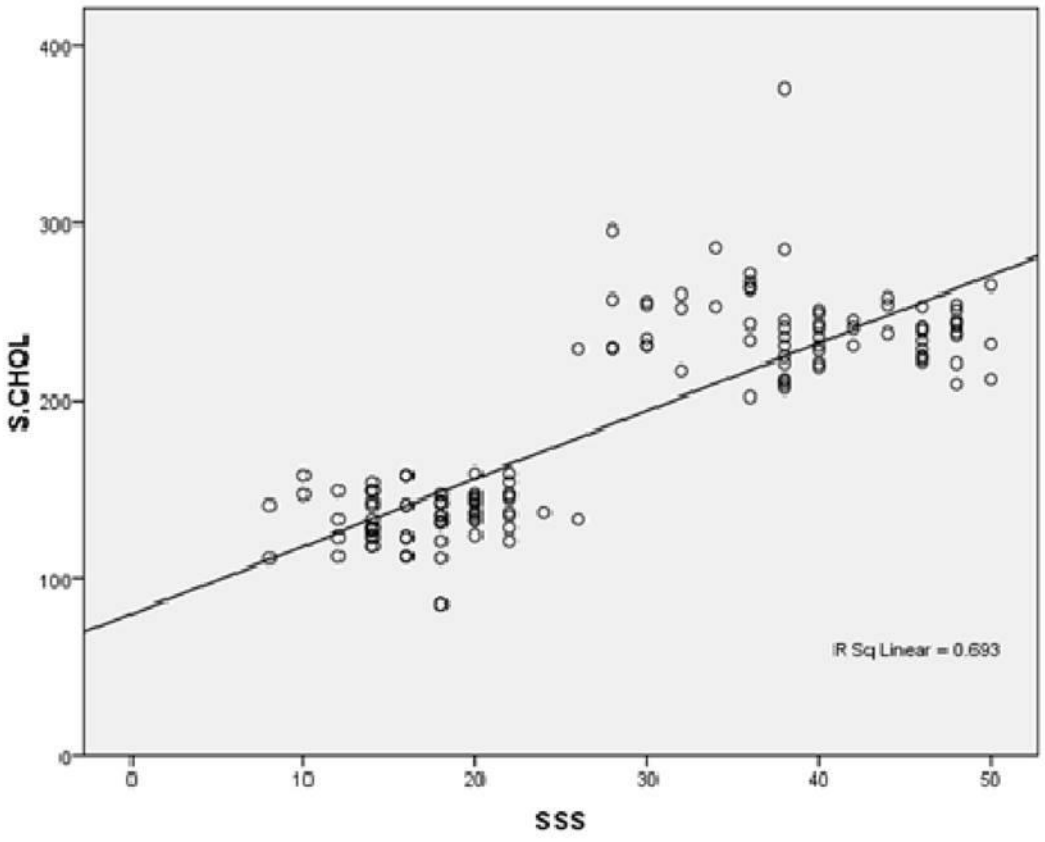
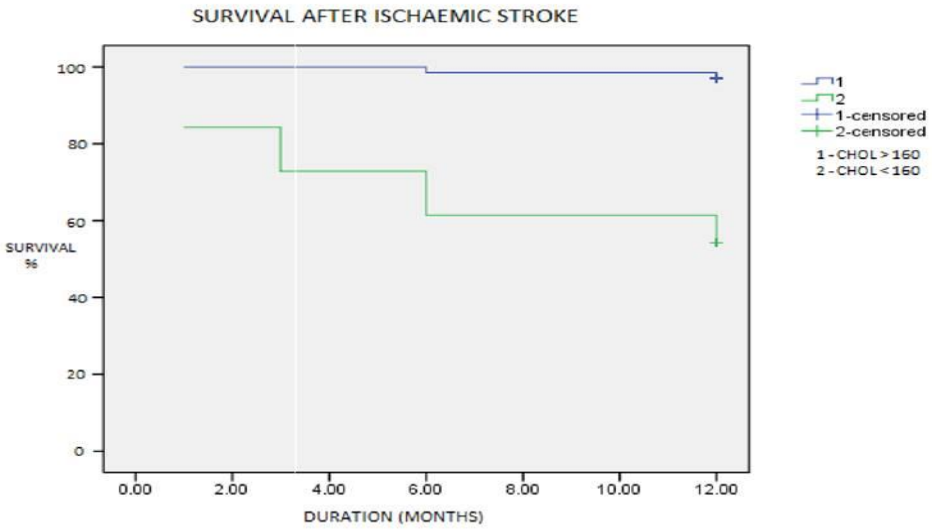


Table - 5: Logistic regression.

VARIABLES	B VALUE	EXP(B)	P VALUE	95% C.I.
AGE	0.191	**1.21**	**p=0.001**	**1.0-1.3**
SEX (MALE,FEMALE)	1.72	5.62	p=0.112	0.67-47.2
DM (YES,NO)	0.407	1.502	p=0.540	0.4-5.5
HYPERTENSION (YES,NO)	0.28	1.32	p=0.73	0.27-6.48
SMOKING (YES,NO)	0.024	1.025	p=0.981	0.13-7.9
ALCOHOLISM (YES,NO)	-0.374	0.688	p=0.695	0.1-4.4
AF (YES,NO)	0.977	2.656	p=0.384	0.29-23.9
S.CHOL(CHOL>160,CHOL<160)	-7.144	0.001	p<0.001	0.00-0.011

Figure - 2: Kaplan-Meier survival -showing the percentage of survival against duration among the two groups of patients.



Discussion

In this hospital based prospective follow up study, the mean age of presentation was 63.4±11.9 years (p=0.534, no statistical significance between groups) which was comparatively lower than other studies [4].This may be due to the early exposure of risk factors of the study population with the comparative studies. There were 13 patients (9.2%) under the age of 45 years which is nearly the same as the incidence of young stroke in comparative studies (10.15%) [5].

Out of 140 patients participated in the study, 75 patients (53.5%) were males and 65 patients (46.5%) were females (p=0.611, no statistical significance between groups). Globally men have a higher incidence of ischaemic stroke than women, but the sex difference of incidence is not statistically significant [6].But in few studies, females had a slightly increased incidence [4].

78 patients were diabetic (55.7%) among the 140 patients participated in the study (p=0.496, no statistical significance between groups). This is much higher than the global prevalence of diabetes in patients developing stroke because the prevalence of diabetes is higher in India. In a study done in US, there was only 33% prevalence of diabetes in stroke patients. Another study showed 37-42% prevalence of diabetes in

stroke patient [7, 8]. In the Copenhagen stroke study only 16.9% had diabetes.

102 patients (72.9%) were hypertensives among the 140 patients in our study, which shows hypertension as the prime risk factor for stroke (p=1.00, equal prevalence between groups). But prevalence of hypertension is nearly twice as high as the prevalence in the comparative studies. The study by Staessen, et al. highlighted that hypertension is causally involved in 70% of strokes [9].

50 patients (35.7%) were smokers among the 140 patients participated in the study (p=0.48, no statistical significance between groups). Studies show that about 25% of strokes were directly attributable to cigarette smoking and it also increases the relative risk by 3 times. In the Copenhagen stroke study, 44.4% of patients were smokers [10].

31 patients were alcoholics (22.1%) in our study group (p=0.839, no statistical significance between groups). In a study done by Oslen, et al.30.9% were alcoholics among the patients who developed stroke [10]. Diabetes and Hypertension are significantly higher in our study group as compared to western population, whereas smoking and alcoholism are lower compared with western population.

20 patients (14.3%) had atrial fibrillation among the 140 patients participated in the study (p=0.05). There is statistically significant difference in the distribution of atrial fibrillation between the groups. A higher incidence of atrial fibrillation is seen in the low cholesterol group. In a study by Jorgensen HS et al 18% of patients had atrial fibrillation.[11] 17.2% patients had atrial fibrillation in the study by Oslen, et al. [10].

The Scandinavian Stroke Scale(SSS) with a score of 0 to 58 was used to assess the clinical severity during admission and low score indicates severe strokes. The mean score of 140 patients was 28.3±12.5 (p<0.001, t value = 25.009, 95% C.I. 20.81-24.38). There is high statistical significance between the means of the groups. The high cholesterol group has a significantly higher mean (39.63) compared to the low cholesterol group (17.03) which showed that the low cholesterol group patients had clinically severe strokes at the time of presentation. In a study done by Boysen G, et al. SSS score ≤ 25 indicated major stroke, whereas a score > 25 indicated mild or moderate stroke [12]. In study done by Oslen, et al. the mean value of SSS score was 39±17 [10].

The patients were followed up for one year and the outcome at the end of one year was measured using modified Rankin scale which has values from 0 to 6. 0 – No symptoms at all, 6 – Death. Every patient in our study had at least minimal deficit at the end of one year, so the patients at the end of 1 year did not have values of 0 and 1 at the end of one year.

Many studies have suggested a modified Rankin scale value of 3 or more as poor outcome [13-15]. So taking a scale of more than 3 as poor outcome, 51 patients out of 70 in the high cholesterol group had a score less than 3 in the high cholesterol group, whereas only 2 out of 70 patients in the low cholesterol group had a score less than 3. The distributions of outcome variables were highly statistically significant between the groups (p<0.001, Chi-square value – 93.83).

At the end of one year follow up, 106 patients were alive and 34 were dead. Only 2 patients expired in the high cholesterol group, compared to 32 patients in the low cholesterol group. This is mainly because; larger infarcts were seen in the low cholesterol group. Similar to the outcome, mortality was also higher in the low cholesterol group with high statistical significance. (95% C.I. 6.5-126.1, OR-28.6, Chi-square value - 34.96, p<0.001).

Serum Cholesterol was positively correlated to SSS score, using bivariate correlation with the Pearson correlation value of 0.832 which shows a high positive correlation, with high statistical

significance (p<0.001)in our study , which means with increasing cholesterol levels increases SSS score which has favourable outcome.

For adjustment of risk factors like DM, Hypertension, Smoking, Alcoholism and AF, serum cholesterol was found to be associated with minor strokes, with B value of -7.144 with a high statistical significance (p<0.001). The Copenhagen stroke study also concluded similarly. Age was found to have a causal relationship, and it showed increasing age causes poor outcome with B value of 0.191 with statistical significance p=0.001. Multiple studies have shown that increased age at stroke onset has grave prognosis [16].

Kaplan – Meier survival analysis showed 1 year survival of 97% in the high cholesterol group and 54% in the low cholesterol group. Multiple studies have shown that patients with high cholesterol levels have better outcome in ischaemic stroke [10].These studies have suggested the neuroprotective role of cholesterol, as the explanation. Adding to it, several large scale studies have shown low cholesterol levels are associated with higher all-cause mortality.[17] Hence the findings of our study may contribute to the explanation of the studies above, as higher cholesterol levels predisposed to minor subtypes of strokes and had better outcome and reduced mortality.

Conclusion

Hypercholesterolemia was found to be a risk factor mainly for the minor subtype of strokes. Higher cholesterol levels favours the development of minor strokes, and hence associated with better outcome. Patients with lower cholesterol levels develop major strokes, therefore had poorer outcome and increased mortality. Hence serum cholesterol levels are inversely related to stroke severity and outcome, and are associated with increased mortality.

References

1. Pandian JD, Sudhan P. Stroke Epidemiology and Stroke Care Services in India. J Stroke, 2013 Sep; 15(3):128–34.
2. Khadilkar SV. Neurology: The Scenario in India. JAPI, 2012 Jan; 60:42–4.
3. Koton S, Molshatzki N, Bornstein NM, Tanne D. Low cholesterol, statins and outcomes in patients with first-ever acute ischemic stroke. Cerebrovasc Dis Basel Switz., 2012; 34(3):213–20.
4. Zuliani G, Cherubini A, Atti AR, Blè A, Vavalle C, Di Todaro F, et al. Low cholesterol levels are associated with short-term mortality in older patients with ischemic stroke. J Gerontol A BiolSci Med Sci., 2004 Mar; 59(3):293–7.
5. Prasad K, Singhal K. Stroke in young: An Indian perspective. Neurol India, 2010; 58(3):343–50.
6. Bogousslavsky J, Pierre P. Ischemic stroke in patients under age 45. NeurolClin., 1992 Feb; 10(1):113–24.
7. Khoury JC, Kleindorfer D, Alwell K, Moomaw CJ, Woo D, Adeoye O, et al.Diabetes mellitus: a risk factor for ischemic stroke in a large biracial population. Stroke J Cereb Circ., 2013 Jun; 44(6):1500–4.
8. Kissela BM, Khoury J, Kleindorfer D, Woo D, Schneider A, Alwell K, et al. Epidemiology of ischemic stroke in patients with diabetes: the greater Cincinnati/Northern Kentucky Stroke Study. Diabetes Care, 2005 Feb; 28(2):355–9.
9. Staessen JA, Kuznetsova T, Stolarz K. Hypertension prevalence and stroke mortality across populations. JAMA, 2003 May 14; 289(18):2420–2.
10. Olsen TS, Christensen RHB, Kammersgaard LP, Andersen KK. Higher total serum cholesterol levels are associated with less severe strokes and lower all cause mortality: ten-year follow-up of ischemic strokes in the

Copenhagen Stroke Study. Stroke J Cereb Circ., 2007 Oct; 38(10):2646–51.

11. Jørgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Acute stroke with atrial fibrillation. The Copenhagen Stroke Study. Stroke J Cereb Circ., 1996 Oct; 27(10):1765–9.
12. Boysen G, Christensen H. Stroke severity determines body temperature in acute stroke. Stroke J CerebCirc,. 2001 Feb; 32(2):413–7.
13. Rådholm K, Arima H, Lindley RI, Wang J, Tzourio C, Robinson T, et al. Older age is a strong predictor for poor outcome in intracerebral haemorrhage: the INTERACT2 study. Age Ageing., 2015 May; 44(3):422–7.
14. Sarraj A, Albright K, Barreto AD, Boehme AK, Sitton CW, Choi J, et al.Optimizing prediction scores for poor outcome after intra-arterial therapy in anterior circulation acute ischemic stroke. Stroke J Cereb Circ., 2013 Dec; 44(12):3324–30.
15. Synhaeve NE, Arntz RM, Maaijwee NAM, Rutten-Jacobs LCA, Schoonderwaldt HC, Dorresteijn LDA, et al. Poor long-term functional outcome after stroke among adults aged 18 to 50 years: Follow-Up of Transient Ischemic Attack and Stroke Patients and Unelucidated Risk Factor Evaluation (FUTURE) study. Stroke J Cereb Circ., 2014 Apr; 45(4):1157–60.
16. Chen R-L, Balami JS, Esiri MM, Chen L-K, Buchan AM. Ischemic stroke in the elderly: an overview of evidence. Nat Rev Neurol., 2010 May;6(5):256–65.
17. Tuikkala P, Hartikainen S, Korhonen MJ, Lavikainen P, Kettunen R, Sulkava R, et al. Serum total cholesterol levels and all-cause mortality in a home-dwelling elderly population: a six-year follow-up. Scand J Prim Health Care, 2010; 28(2):121–7.