Original article

Determinants of dysphagia following stroke

Kumaresan A[1*], JagatheesanAlagesan[2], VijayaraghavanR[3], ArunachalamRamachandran[4], Manoj Abraham M[5], Geetha.M[6]

Abstract

Background: Swallowing is affected following stroke. Many studies focus on various aspects of swallowing difficulties (dysphagia) following stroke. However, there are not many studies on the determinants of dysphagia following stroke. The aim of the present study is to establish the association between various factors with the severity of dysphagia.

Methods: After screening for Mann Assessment of Swallowing Ability (MASA),110 patients, post-stroke were selected using consecutive sampling to assess the common risk factors, namely the presence of diabetes mellitus, dyslipidemia, hypertension, alcohol usage and smoking habits. Additionally, other variables such as age, gender, type of lesion, side of lesion, tobacco chewing, speech disorders, arterial dysfunction, lobe involvement and Brunnstrom's stages, were also evaluated using a structured interview method. $\chi 2$ (chi-squared) analysis was carried out to find out the association between the selected determinants and severity of dysphagia following stroke.

Results: It was found that age and Brunnstrom's stages are the determinants of dysphagia, as analysis showed a strong association with a p value < 0.001. A marginal association between post-stroke dysphagia and type of lesion with a p value of 0.056 was also observed.

Conclusions: Among 15 factors evaluated, age, type of lesion and Brunnstrom's stages showed a significant association with the severity of dysphagia following stroke. This study advocates early dysphagia management for elderly patients with high Brunnstrom's grading, for those who are not expected to spontaneously recover following stroke, and for earlier and better community rehabilitation. [*Ethiop.J. Health Dev.* 2019; 33(3):147-152]

Key words: Post-stroke dysphagia, Brunnstrom's stages, dysphagia risk factors.

Introduction

Unlike most human disorders, stroke is not only an individual and familial burden, but an immense social burden (1). In addition to motor, cognitive and sensory problems, swallowing problems also frequently occur following stroke. Studies show that the occurrence of dysphagia is between 25% and 62% (2-5). Previous studies have shown that dysphagia following unilateral stroke is rare, but based on clinical and radiographic studies, it is now accepted that unilateral hemisphere cortical involvement can also lead to stroke (6).Globally, rate of stroke ranged from 105 to 152 in 100,000 people every year between 1960 and 2015, and the unrefined pervasiveness of stroke ranged from 44.29 to 559 in 100,000 people in various parts of India (7). Developing countries such as India are facing a double burden of communicable and non-communicable diseases. Stroke is one of the leading causes of death and disability in India. The estimated prevalence rate of stroke ranged from 84 to 262 for 100,000 in rural areas, and 334 to 424 for 100,000 in urban areas. The incidence rate is 119 to 145 for 100,000, based on a population-based study (8).

Stroke is characterized as a neurological problem and attributed to severe damage of the central nervous system (CNS) due to vascular complications, including cerebral localized necrosis, intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). It is a leading condition of morbidity and mortality around the world (9). Advances in basic science, neuropathology and neuroimaging have enhanced the ability to diagnose ischemia, infarction and hemorrhage in the CNS.

About 100 published articles, including 59 incidence studies from 19 countries, revealed that the mean age at first stroke was 68.6 years among men, and 72.9 years among women. Gender-related stroke incidence revealed that the stroke rate among males was 33% higher and the prevalence was 41% higher than among females (10). Risk factors of stroke were classified as non-modifiable, modifiable and potentially modifiable factors (11, 12). Non-modifiable risk factors are age, sex, race/ethnicity, and genetic factors. Well-documented and modifiable risk factors consist of hypertension, exposure to cigarette smoke, diabetes, certain other cardiac conditions, dyslipidemia, physical inactivity and obesity. Less well-documented and potentially modifiable risk factors include metabolic syndrome, alcohol abuse and drug abuse (13,14).

Hypertension is the single most important risk factor for stroke. It is a modifiable risk factor that increase with age. Hypertensives above 80 years of age has 90% probability of risk of developing stroke (13,15,16). Smoking can block the blood vessels and subsequently damage them. The risk of stroke is 50% higher in smokers compared to non-smokers. Smoking is a preventable risk factor. Approximately 20% of the adult population continues to smoke and the risk continues throughout life in both genders and in various racial groups (14).

[1,2]Saveetha college of Physiotherapy, SIMATS, Chennai-602105. Email: kresh49@gmail.com
[3]Director of Research and Development, SIMATS, Chennai-602105
[4]Madhav University, Rajasthan
[5]Faculty of Medicine and Health Sciences, UniversitiTunku Abdul Rahman, Malaysia
[6]Director, GNK Dental Clinic, Walajapet-632513

Diabetes (type 1 and type 2) doubles the risk of stroke. High cholesterol level increases the risk of blocked arteries. If an artery leading to the brain becomes blocked, stroke can result. Being inactive and obese can increase the risk of heart disease and stroke (17).
Cerebral, cerebellar and brain stem strokes can impair swallowing mechanism (18). Cerebral lesions can interrupt voluntary control of mastication and bolus transport during the oral phase. Cortical lesions involving the precentralgyrus may produce contralateral impairment in facial, lip and tongue motor control. This may also compromise pharyngeal peristalsis. Cerebral lesions causing impairments in cognitive function, such as concentration or selective attention, may also impair control of swallowing. Brain stem strokes are less common than cortical lesions, but both may cause swallowing complications (19,20). Brain stem lesions can affect sensation of the mouth, tongue, cheek, timing in the trigger of the pharyngeal swallow, laryngeal elevation, glottis closure and cricopharyngeal relaxation (21).

Dysphagia is one of the complications immediately after stroke in the acute phase. Although the risk factors of stroke were analyzed in previous studies, they were not associated with the severity of dysphagia. Hence, in this study, the main objective was to analyze the influence of selected determinants in the severity of dysphagia among post-stroke dysphagia.

Methods

Sampling method and sample size determination: The study duration was four months from December 2016 to March 2017. All the patients who participated in the study were recruited when they attended hospital for acute care. The subjects who fulfilled the inclusion and exclusion criteria, including MASA screening, were recruited for the study. After assessment by MASA scale of swallowing ability scoring sheet, 110 post-stroke individuals were recruited. The patients in the study were categorized into group 1, group 2 and group 3 based on the severity of dysphagia, namely mild, moderate and severe, according to the MASA scale (22).

Data collection procedure: All the socio-demographic data were collected from the patients. The participants of the study were screened for the 15 variables such age, gender, body mass index, side and type of lesion, hypertension, dyslipidemia, type 2 diabetes mellitus, aphasia, tobacco chewing, smoking, alcohol, arterial dysfunction, lobe of lesion and Brunnstrom's stages. The 110 study patients recruited for the treatment were assessed for various risk factors. The patients visited the hospital at varying daysafter their stroke: 78% were evaluated after seven to 10 days, 18% after 11 to 13 days, and 4% after 14 and 15 days, following stroke.

Data analysis: Data were entered and analyzed using SigmaPlot 13 statistical package (Systat software, USA). $\chi 2$ (chi-squared) test was used to find the association between severity of dysphagia and the risk factors. A probability of 0.05 or less was considered as statistically significant.

Study design and setting: A prospective, cross-sectional, descriptive, analytical study was conducted at Saveetha Institute of Medical and Technical Sciences (Chennai, India).

Eligibility criteria:The inclusion criterion was both genders with complaints of stroke, either ischemic or hemorrhagic. Patients presenting any other neurological or structural changes, such as pneumonia, chest complications and inflammatory conditions that might interfere with swallowing process, were excluded from the study. Those who showed spontaneous recovery within seven days were also excluded.

Ethical consideration: This study was approved by the Institutional Human Ethics Committee (015/02/2017/IEC/SU) of Saveetha Medical College and Hospital (Chennai, India) as per the guidelines of the Indian Council of Medical Research (New Delhi, India).

Results

Socio-demographic characteristics:The age range of the study population was 36 to 95 years. Two-thirds (66.3%) were male, and a third (33.7%) were female. Clinically, 31% were brought in on a stretcher, 43% were assisted by companions, 16% were supported by walking sticks, and the remaining 10% walked unassisted.

Factors associated with stroke:The $\chi 2$ analysis of age showed a strong association with the severity of dysphagia ($p<0.001$). In the mild category, 28%, 47% and 25% were in the age group of <50 years, 50-70 years and >70 years, respectively. In the moderate category, 23.2%, 57.1% and 19.6% were in the age group of <50 years, 50-70 years and >70 years, respectively. In the severe category, 0% were in the age groups of<50 years and 50-70 years, and 0.07% in the >70 years age group, hence showing severe dysphagia in the>70 years category.

The association between Brunnstrom's grading and severity of dysphagia was also significant ($p<0.001$). In the mild category, 19.6% and 73.9% were in the Brunnstrom stages 1-3 and 4-6 respectively. In the moderate category, 67.9% and 26.8% were in the above categories respectively. In the severe category, 87.5% were in stages 1-3.

The type of lesion with dysphagia showed a marginal significant association ($p = 0.056$). The types of lesion were classified as hemorrhagic and ischemic. The mild category showed 46% for hemorrhagic and 54% for ischemic. The moderate category showed 24% for hemorrhagic and 76% for ischemic. The severe category showed 37% for hemorrhagic and 63% for ischemic. All the other variables showed no association with the severity of dysphagia, as illustrated in Table 1 and Table 2. The other p values ranged from 0.231 to 0.896.

Table 1**: Risk factors of stroke and its influence on post-stroke sysphagia (n=110)**

Risk factor	Category	Mild	Moderate	Severe	Statistics
Alcohol use	Yes	18	15	3	χ^2=1.736
	No	26	38	5	P = 0.420
Smoking	Yes	14	15	4	χ^2=1.524
	No	30	38	4	P = 0.467
Tobacco chewin	Yes	9	17	3	χ^2= 2.931
	No	35	38	3	P = 0.231
Hypertension	Yes	17	26	4	χ^2 = 1.112
	No	29	30	4	P = 0.573
Diabetes mellitus	Yes	20	30	4	χ^2 = 1.032
	No	26	29	4	P = 0.597
Dyslipidaemia	Yes	18	18	3	χ^2 = 0.555
	No	28	38	5	P = 0.758

Table 2**: Various factors and its influence on post-stroke dysphagia (n=110)**

Risk factor	Category	Mild	Moderate	Severe	Statistics
Age	Below 50 years	13	13	0	χ^2 = 23.322
	50-70 years	21	32	0	P<0.001
	Above 70 years	12	11	8	
Gender	Male	29	38	6	χ^2 = 0.550
	Female	17	18	2	P = 0.759
BMI	Normal (18.5–24.9)	15	19	3	χ^2 = 1.086
	OW (25–29.9)	17	23	2	P = 0.896
	Obese (30 or more)	14	14	3	
Lobe involvement	Single	22	32	4	χ^2 = 0.905
	More than one lobe	24	24	4	P = 0.636
Side of lesion	Right	21	26	2	χ^2 = 1.340
	Left	25	30	6	P = 0.512
Type of lesion	Hemorrhage	21	13	3	χ^2 = 5.754
	Ischemia	25	43	5	P = 0.056
Arterial dysfunction	ACA	8	7	2	χ^2 = 7.560
	ICA	4	7	0	P = 0.272
	MCA	23	24	3	
	PCA	9	2	2	
Speech dysfunction	Broca's aphasia	5	6	3	χ^2 = 7.514
	Wernicke's aphasia	3	8	1	P = 0.276
	Conduction aphasia	3	5	1	
	Normal	35	37	3	
Brunnstrom's stages	stage 1-3	9	38	7	χ^2 = 23.322
	stage 4-6	34	15	0	P<0.001

OW=overweight, ACA=anterior cerebral artery, ICA=internal carotid artery, MCA=middle cerebral artery, PCA=posterior cerebral artery. χ^2 =chi-squared

Discussion

Stroke is recognized as a leading cause of morbidity and mortality worldwide in developed countries and is associated with various complications leading to prolonged hospitalization and significant health care costs (23). Though many stroke patients after recovery show normal swallowing, 11% to 50% still had dysphagia after six months (21). The optimal management of post-stroke dysphagia, including diagnosis, investigation, treatment and prognosis, remains to be defined. In this cross-sectional study, 15 different factors were selected and analyzed for their influence on the severity of dysphagia following stroke. These factors were selected as they were influencing stroke and other cardiovascular disorders (13–15). A study identified that old age, hypertension, diabetes, cardiac problems, alcohol intake and cigarette smoking influenced stroke, and indicated that hemorrhagic stroke was 59.4% and ischemia was 40.6% (24). The major findings for the current scenario are poor adherence to drug regimen and uncontrolled high blood pressure (24). Dysphagia is a major concern following stroke which may lead to aspiration of food, fluid and oral secretions. These aspirated contents are potential source of pneumonia. (25). Other studies have conducted analysis of dysphagia associated with acute cervical spinal cord injury (26).

Age is considered to be an important criterion in dysphagia, as there are studies which show that the swallowing function reduces even in normal individuals of higher age (27). There are reports that swallowing becomes difficult due to insufficient breathing patterns with reduced tidal volume in old people. Thus, an analysis of the age factor was included in this study by categorizing the age group into three categories: below 50 years, 50 to 70 years and more than 70 years. The analysis showed that there is a strong association between age and severity of post-stroke dysphagia. People who were younger than 50 years old had a less severe form of post-stroke dysphagia compared to the other two groups, indicating that older people are vulnerable to severe dysphagia following stroke. A study of swallowing difficulty in apnea related to lingual bolus propulsion in adults showed that gender did not influence the swallowing function, but age had an association (28). Hence, gender was analyzed in the present study. The results showed that gender had no significant involvement.

The severity of dysphagia is significantly related to stroke lesions of the brain stem and bilateral hemispheres (29). Previous studies have identified patterns of lesion that can predict dysphagia after acute stroke (30). However, these studies were limited to the acute period following stroke. Moreover, lesions which were outside of the brain stem have not been investigated in chronic dysphagia. Analysis made of cerebrovascular accidents with unilateral involvement shows that at least 40% of the people had dysphagia. Swallowing requires complex neuromuscular activity, and unilateral hemispheric damage can also lead to dysphagia after stroke (21). In the present study, the severity of post-stroke dysphagia with cerebral origin was analyzed with anatomical variables such as the side of the lesion (right and left cerebrovascular accident), location of the lesion, lobe involved, and arterial territories involved.

The analysis of side of involvement showed that there was no association between the CVA side and severity of stroke. Equal distribution of dysphagia following right and left CVA was observed, though the severity and type of dysphagia consistently differed in both. This may be explained by the fact that swallowing occurs by voluntary (oral) and involuntary (pharyngeal) phases. Hence, damage to voluntary and involuntary components of neurological function can affect dysphagia after a stroke. Further, swallowing utilizes bi-hemispheric components of neurological function (31). The type of stroke categorized as ischemic and hemorrhagic influenced the severity of post-stroke dysphagia, with ischemic stroke showing severe dysphagia. This analysis was done with anterior cerebral artery, middle cerebral artery, posterior cerebral artery and internal carotid artery using computed tomography reports of the patients.

The analysis of lobe involved was categorized as frontal, fronto-parietal, parietal, parieto-occipital, occipital, occipital. The analysis showed that there was no single lobe that dominated the influence of dysphagia severity. An analysis was also conducted to find out whether the number of lobes involved had an impact on the severity of dysphagia. This analysis also showed that, irrespective of the number of lobes involved, the severity of dysphagia remained the same.

Previous findings suggest that 10 risk factors are associated with 90% of the risk of stroke, which includes tobacco chewing, smoking and alcohol use. Targeted interventions that reduce blood pressure and smoking, and promote physical activity and a healthy diet, could substantially reduce the burden of stroke (32). Studies also showed that tobacco chewing, smoking and alcoholic neuropathy with post-stroke dysphagia resulted in pneumonia. In the present study, the severity of post-stroke dysphagia was assessed for association with tobacco chewing habits for at least 10 years, smoking and alcoholic symptoms. The analysis showed that none of the three risk factors had an influence on the severity of dysphagia.

Lifestyle disorders and metabolic disorders have many things in common. Both are modifiable risk factors for stroke. Epidemiologic studies have shown that diabetes, which is the most common metabolic disorder, is a well-established independent but modifiable risk factor for stroke of both types, ischemic and hemorrhagic (32). Similarly, hypertension has proved to be an important modifiable risk factor and also an important prognostic tool in the management of stroke (33). Blood pressure also determines the compliance with treatment and development of complications (34). Analysis of hypertension, diabetes mellitus and dyslipidemia showed that there was no association with severity of dysphagia.

The level of spasticity in stroke is an important component of motor recovery. An analysis was carried out to establish whether the stage of spasticity evaluated by Brunnstrom's grading influenced dysphagia. The analysis showed that patients who had increased levels of spasticity (grading 1-3) did have severe dysphagia, which is an indication of the lack of voluntary control of muscles.The study also analyzed body mass index and aphasia as a criterion for the severity of dysphagia and the results showed that there was no significant influence.

Conclusions

This study shows that out of the 15 criteria analyzed, only age, type of lesion and levels of spasticity graded by Brunnstrom's stages had an influence on dysphagia severity following stroke. This study advocates early dysphagia management for older people, dysphagia following ischemic stroke, and patients with high Brunnstrom's grading who are not expected to make a spontaneous recovery. Early intervention can prevent residual post-stroke dysphagia.

Competing interests

The authors declare that they have competing interests. This study was not funded.

References

1. Ekberg O, Hamdy S, Woisard V, Wuttge-Hannig A, Ortega P. Social and psychological burden of dysphagia: its impact on diagnosis and treatment. Dysphagia. 2002 Sprint; 17(2): 139-46
2. Mann G, HankeyGJ, Cameron D. Swallowing disorders following acute stroke: prevalence and diagnostic accuracy. Cerebrovasc Dis. 2000;10(5):380-6.
3. Smithard D, O'Neill P, England R, Park CL, Wyatt R, Martin DF, Morris J. The natural history of dysphagia following a stroke. Dysphagia. 1997;12(4):188-93.
4. Ramsey D, Smithard D, Kalra L. Silent aspiration: what do we know? Dysphagia.2005; 20(3):218-25.
5. Falsetti P, Acciai C, Palilla R, Bosi M, Carpinteri F, Zingarelli A, *et al.*Oropharyngeal dysphagia after stroke: incidence, diagnosis, and clinical predictors in patients admitted to a neurorehabilitation unit. Cerebrovasc Dis. 2009;18(5):329-35.
6. Cohen DL, Roffe C, Beavan J, Blackett B, Fairfield CA, Hamdy S, *et al.* Post-stroke dysphagia: a review and design considerations for future trials. International Journal of Stroke. 2016;11(4):399-411.
7. Kamalakannan S, AashraiSV, GudlavalletiVS, Gudlavalleti M, Goenka S, Kuper H. Incidence and prevalence of stroke in India: a systematic review. Indian J Med Res. 2017;146(2):175-85.
8. Pandian JD, Sudhan P. Stroke epidemiology and stroke care services in India.J Stroke. 2013;15(3):128-34.
9. Temesgen TG, Teshome B, Njogu P. Treatment outcomes and associated factors among hospitalized stroke patients at Shashemene Referral Hospital, Ethiopia. Stroke Research and Treatment. 2018;1:1-5.
10. Kelly-Hayes M. Influence of age and health behaviors on stroke risk: lessons from longitudinal studies. Journal of American Geriatric Society. 2010;58(2):S325-8.
11. Wolf PA, D'AgostinoRB, O'Neal MA, Sytkowski P, Kase CS, Belanger AJ, *et al.* Secular trends in stroke incidence and mortality: The Framingham Study. Stroke. 1992; 23(11):1551-5.
12. Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Stroke incidence, prevalence, secular trends in Rochester, Minnesota, through 1989. Stroke. 1996;27(3):373-80.
13. Mulat B, Mohammed J, Yeseni M, Alamirew M, Dermello M, Michael NG, *et al.* Magnitude of stroke and associated factors among patients who attended the medical ward of FelegeHiwot Referral Hospital, Bahir Dar town, northwest Ethiopia. Ethiopian Journal of Health Development.2016;30(3):129-34.
14. Goldstein LB. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: the American Academy of Neurology affirms the value of this guideline.Stroke. 2006;37(6):1583-633.
15. Zia E, Hedblad B, Pessah-Rasmussen H, Berglund G, Janzon L, Engstrom G. Blood pressure in relation to the incidence of cerebral infarction and intracerebral hemorrhage. Hypertensive hemorrhage: debated nomenclature is still relevant. Stroke. 2007;38(10):2681-5.
16. Song YM, Sung J, Lawlor DA, Davey Smith G, Shin Y, Ebrahim S. Blood pressure, haemorrhagic stroke, and ischaemic stroke: the Korean national prospective occupational cohort study. BMJ. 2004;328(7435):324-5.
17. TunNN, Arunagirinathan G, Munshi SK, Pappachan JM. Diabetes mellitus and stroke: a clinical update. World J Diabetes. 2017;8(6):235-48.
18. Hamdy S, Aziz Q, RothwellJC, Singh KD, Barlow J, Hughes DG, *et al.* The cortical topography of human swallowing musculature in health and disease. Nat Med. 1996;2(11):1217-24.
19. Schroeder MF, Daniels SK, McClain M, Corey DM, Foundas A. Clinical and cognitive predictors of swallowing recovery in stroke. J Rehabil Res Dev. 2006;43(3):301-10.
20. Moon HI, Pyun SB, Kwon HK. Correlation between location of brain lesion and cognitive function and findings of video fluoroscopic swallowing study. Ann Rehabil Med. 2012; 36(3):347-55.
21. Smithard DG, O'Neill PA, Park C. Complications and outcome after acute stroke. Does dysphagia matter? Stroke. 1996;27:1200-4.
22. Edmiaston J, Connor LT, Loehr L, Nassief A. Validation of a dysphagia screening tool in acute stroke patients. Am J Crit Care. 2009;19(4):357-64.
23. Mozzafarian D, Benjamin EJ, Go AS, Arnett DK, BlahaMJ, Cushman M, *et al.,* on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics – 2016 update: a report from the American Heart Association. Circulation.2016;133(4):e38-360.
24. ErkabuSG, Agedie Y, Mihretu DD, Semere A, AlemuYM. Ischemic and hemorrhagic stroke in Bahir Dar, Ethiopia: a retrospective hospital-based Study. J Stroke Cerebrovasc Dis. 2018;27(6):1533-8.
25. Wilson RD. Mortality and cost of pneumonia after stroke for different risk groups. J Stroke Cerebrovasc Dis. 2012;21:61-7.
26. Hayashi T, Fujiwara Y, Sakai H, Maeda T, Ueta T, Shiba K. Risk factors for severe dysphagia in acute cervical spinal cord injury, Spinal Cord. 2017;55(10):940-3.
27. Wang C, Chen J, Chuang C. Aging-related changes in swallowing, and in the coordination of swallowing and respiration determined by novel non-invasive measurement techniques. GeriatrGerontol Int. 2015;15(6):736-44.
28. Hiss SG, Strauss M, Treole K, Stuart A, Boutilier S. Effects of age, gender, bolus volume, bolus

viscosity, and gustation on swallowing apnea onset relative to lingual bolus propulsion onset in normal adults. J Speech Lang Hear Res. 2004;47(3):572-83.

29. Daniels SK, Foundas AL, Iglesia GC, Sullivan MA. Lesion site in unilateral stroke patients with dysphagia. J Stroke Cerebrovasc Dis. 1996;6(1):30-4.

30. Galovic M, Leisi N, Muller M, Weber J, Abela E, Kagi G, *et al.* Lesion location predicts transient and extended risk of aspiration after supratentorial ischemic stroke. Stroke. 2013;44(10):2760-7.

31. Ertekin C. Voluntary versus spontaneous swallowing in man. Dysphagia. 2011;26(2):183-2.

32. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, *et al.* Risk factors for ischaemic and intracerebralhaemorrhagic stroke in 22 countries (the INTERSTROKE Study): a case-control study. Lancet. 2010;376(9735):112-23.

33. Potter JF, Robinson TG, Ford GA, Mistri A, James M, Chernova J, Jagger C. Controlling hypertension and hypotension immediately post-stroke: a randomized, placebo-controlled, double-blind pilot trial. The Lancet Neurology.2009;8(1):48-56.

34. Zhao JL, Du ZY, Sun YR, Yuan Q, Yu J, Wu X, *et al.* Intensive blood pressure control reduces the risk of progressive hemorrhage in patients with acute hypertensive intracerebral hemorrhage: a retrospective observational study.Clinical Neurology and Neurosurgery.2019;180:1-6.