

Low Baseline Urine Creatinine Excretion Rate Predicts Poor Outcomes among Critically Ill Acute Stroke Patients

Chia-Yu Hsu¹, Yi-Ling Wu¹, Chun-Yu Cheng¹, Jiann-Der Lee¹, Ying-Chih Huang¹, Ming-Hsueh Lee¹, Chih-Ying Wu¹, Huan-Lin Hsu¹, Ya-Hui Lin¹, Yen-Chu Huang¹, Hsin-Ta Yang¹, Jen-Tsung Yang¹, Meng Lee^{1,*} and Bruce Ovbiagele²

¹Departments of Neurology and Neurosurgery, Chang Gung University College of Medicine, Chang Gung Memorial Hospital, Chiayi, Taiwan

²Department of Neurosciences, Medical University of South Carolina, Charleston, South Carolina, USA



Abstract: Urinary creatinine excretion rate (CER) is an established marker of muscle mass. Low CER has been linked to poor coronary artery disease outcomes, but a link between CER and acute stroke prognosis has not been previously explored. We prospectively collected data from patients with acute stroke (ischemic or hemorrhagic) within 24 hours from symptom onset in a Neurological and Neurosurgery Intensive Care Unit in Taiwan. Baseline CER (mg/d) was calculated by urine creatinine concentration in morning spot urine multiplies 24-hour urine volume on the second day of admission. Patients were divided into 3 tertiles with highest, middle, and lowest CER. Primary endpoint was poor outcome defined as modified Rankin Scale 3-6 at 6 months. Among 156 critically ill acute stroke patients meeting study entry criteria, average age was 67.9 years, and 83 (53.2%) patients had ischemic stroke. Patients with lowest CER (vs. highest CER) had a high risk of poor outcome at 6-month after adjustment (odds ratio 4.96, 95% confidence interval 1.22 to 20.15, p value = 0.025). In conclusion, low baseline CER, a marker of muscle mass, was independently associated with poor 6-month outcome among critically ill acute stroke patients. We speculate that preservation of muscle mass through exercise or protein-energy supplement might be helpful for improving prognosis in severe stroke patients.

Keywords: Urine creatinine excretion rate, stroke, critically ill, outcome.

INTRODUCTION

Obesity is a surging epidemic worldwide. Although obesity is a known risk factor for primary cardiovascular events including stroke [1], its contribution to recurrent vascular risk [2] and prognoses following an acute vascular event remain controversial [3]. Indeed, several studies indicate that a so-called “obesity paradox” might exist because outcomes after an index vascular event (including stroke) appear to be better for obese patients compared to their lean counterparts [4].

While several potential underlying mechanisms have been proposed for the obesity paradox, a major critique of data supporting the notion of such a paradox has been the use of body mass index (BMI) as the index of obesity. Since BMI does not differentiate body composition into muscle, bone or adipose tissue, it is increasingly viewed as an inadequate measure of unhealthy body habitus. On the other hand, urinary creatinine excretion rate (CER) is an established marker of muscle mass [5]. Over 98% of endogenous creatinine comes from skeletal muscle, which is

then excreted into urine at a constant rate. Therefore, urinary CER is proportional to muscle mass, roughly 17-20 kilograms of muscle per 1 gram of creatinine. [5] In fact, low CER is an independent predictor of cardiovascular disease and mortality in the general population [6], and has also been associated with higher all-cause mortality in patients with coronary artery disease [7].

Little is known about the role of CER as a prognosticator in stroke patients. In this study, we aimed to assess the relationship of CER with outcome among critically ill acute stroke patients.

METHODS

Study Participants and Clinical Assessment

We prospectively collected data on consecutive patients with acute stroke within 24 hours from symptom onset and admitted to a Neurological and Neurosurgery Intensive Care Unit in a hospital in Taiwan from September 1, 2007 to August 31, 2010. Established hospital protocol criteria for admission to our Neurological and Neurosurgery Intensive Care Unit included hemodynamic instability, acute respiratory failure or intubation for airway protection, unstable neurologic status or Glasgow coma score (GCS) < 11. Both ischemic stroke and hemorrhagic stroke types were

*Address correspondence to this author at the Chang Gung University College of Medicine, Chang Gung Memorial Hospital, Chiayi, Taiwan, Tel: 86653621000; Fax: +88653623002; E-mail: b8101099@gmail.com

Received: October 27, 2014 Revised: December 14, 2014 Accepted: December 16, 2014

included, but subarachnoid hemorrhage and traumatic intracranial hemorrhage were excluded. Patients with end stage renal disease [defined as estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73m²] or known impairment of functional status [defined as modified Rankin Scale (mRS) ≥ 3] prior to the index stroke were also excluded. Patients who met our criteria were evaluated mRS at 6-month follow-up.

We collected baseline demographic for all patients, including age, sex, and medical history of hypertension, diabetes mellitus, atrial fibrillation and prior cerebrovascular disease. Systolic and diastolic blood pressure values were determined on admission. All patients received brain computerized tomography and/or magnetic resonance imaging for stroke subtypes evaluation. Neurological deficits were evaluated with the National Institute of Health Stroke Scale (NIHSS), and severity of the disease was evaluated with the Acute Physiology and Chronic Health Evaluation II (APACHE-II) score for each patient on admission. Weight and height were measured on admission with subjects in light clothes and without shoes. BMI was calculated as weight in kilograms divided by height in meters squared.

Serum creatinine was obtained during the Emergency Department encounter. eGFR was estimated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation adjusted for Asians [8]. Daily (24-hour) urine volume was recorded by nursing personnel since the admission time to Intensive Care Unit. Urine creatinine concentration was measured by spot morning urine on the second day after admission. CER (mg/day) was calculated as urine creatinine concentration multiplied by 24-hour urine volume. Blood glucose and albumin were obtained on the second day after admission.

The primary outcome measure was death or dependence, defined as a mRS of 3-6 at 6 month after stroke onset. Secondary outcome was death or disability, defined as a mRS of 2-6 at 6 month after stroke onset. Evaluators of 6-month mRS were unaware of patients' in-hospital CER results.

The study was performed under a protocol approved by the Institutional Review Board of Chang Gung Memorial Hospital, and all examinations were performed after obtaining written informed consent from the patients or appropriate family members.

STATISTICAL ANALYSIS

Statistical analyses were performed using the Statistical Program for Social Sciences (SPSS) statistical software (version 18, Chicago, IL, USA). We divided all patients into 3 tertiles with highest, middle and lowest CER. The differences between the three groups were analyzed by Kruskal-Wallis test for skewed variables, Analysis of Variance (ANOVA) for normally distributed variables, and Pearson's Chi Square test for categorical variables. The patients' characteristics according to outcome status were compared by Mann-Whitney U test for skewed variable, Student t-test for normally distributed variables, and Pearson's Chi Square test for categorical variables. Variables with two-tailed *p* value less than 0.05 were considered to be

statistically significant and were included in the regression model. Multivariate-adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association of CER, using highest tertile as a reference, and 6-month outcome was calculated by a logistic regression analysis. The multivariate model included age, sex, baseline NIHSS score, APACHE-II score on admission, history of stroke, albumin and eGFR and classified CER. All *p* values were two-tailed and a *p* value < 0.05 was considered statistically significant.

RESULTS

Among 184 consecutive stroke patients during this period of time, 156 patients met study criteria. Overall, mean age was 67.9 (±13.3) years and 83 (53.2%) patients had ischemic stroke. Median baseline NIHSS score was 16 [interquartile range (IQR) 9-21], and median APACHE-II score on admission was 12 (IQR 9-15). Median urine CER was 1312.4 mg/d (IQR 872.4-1892.1). BMI was obtained from 103 patients, with 29 (28.2%) were overweight (defined as 25 ≤ BMI < 30) and 6 (5.8%) were obese (defined as BMI ≥ 30).

The median CER in the 3 tertiles of highest, middle and lowest CER was 2297.7 mg/d, 1312.4 mg/d and 743.6 mg/d, respectively. A comparison of clinical characteristics in the three groups is shown in Table 1. Patients with the lowest CER were significantly older (*p* < 0.001), more often female (*p* < 0.001), and had lower BMI (*p* < 0.001) when compared with the patients with highest CER.

Also, high baseline NIHSS score, high APACHE-II score, prior stroke, low albumin, and low eGFR were associated with poor outcomes at 6 months. (Table 2).

In the multivariate logistic regression model, lowest CER, as compared to highest CER, was independently associated with higher possibility of death or dependence at 6 month (92.3% vs. 73.1%, OR 4.96, 95% CI 1.22 to 20.15, *p* = 0.025) after adjustment. The result was similar when we used death or disability as the endpoint (Table 3). Middle CER, as compared to highest CER, showed no difference in the possibility of death or dependence at 6 month (75.0% vs. 73.1%, OR 2.24, 95% CI 0.73 to 6.92, *p* = 0.160), but was associated with higher possibility of death or disability at 6 months (88.5% vs. 78.8%, OR 5.74, 95% CI 1.40 to 23.63, *p* = 0.015).

DISCUSSION

In this study, we found that critically ill acute stroke patients in the lowest tertile of CER had greater odds of experiencing death or having severe disability at 6-months post-hospitalization, even after adjusting for confounders. Since CER is a marker of muscle mass, the results of this study suggest that low muscle mass may be an independent predictor of poor outcome after a severe acute stroke.

Some urine biomarkers have been used as prognosticators in cardiovascular and cerebrovascular diseases [9-11]. For example, increased urine albumin and IgM excretion were supposed to reflect general vascular damage and had been linked to poorer functional outcome after stroke,

Table 1. Clinical characteristics of the critically-ill acute stroke patients by tertiles of urinary creatinine excretion rate.

CER Tertiles	Highest (N=52)	Middle (N=52)	Lowest (N=52)	p value
Age, y, mean±SD	62.8±13.7	68.4±12.7	73.3±11.0	<0.001*
Men, n (%)	43 (84.7)	32 (61.5)	21 (40.4)	<0.001*
Stroke subtype and clinical severity				
Ischemic Stroke, n (%)	26 (50.0)	31 (59.6)	26 (50.0)	0.525
Baseline NIHSS, median (IQR)	16.5 (8-21)	14 (7-17.5)	17 (12-22)	0.021*
APACHE-II score, mean±SD	12.1±5.1	11.2±4.4	13.8±5.1	0.022*
Comorbidity, n (%)				
Prior Stroke	11 (21.2)	15 (28.8)	16 (30.8)	0.504
Hypertension	36 (69.2)	33 (63.5)	41 (78.8)	0.221
Diabetes	14 (26.9)	11 (21.2)	12 (23.1)	0.780
Atrial fibrillation	4 (7.7)	5 (9.6)	8 (15.4)	0.424
Physical and lab data at admission				
Systolic blood pressure at admission, mmHg, mean±SD	184.6±35.8	173.0±38.1	175.1±33.5	0.215
Diastolic blood pressure at admission, mmHg, mean±SD	101.8±21.8	97.1±22.2	95.1±22.3	0.288
Blood glucose, mg/dL, mean±SD	155.5±68.8	155.9±73.2	166.7±75.4	0.560
Albumin, mg/dL, mean±SD	3.5±0.6	3.9±0.8	3.6±0.6	0.013*
eGFR, mL/min/1.73m ² , median (IQR)	62.3 (38.4-73.1)	57.0 (48.3-73.2)	58.4 (36.9-69.9)	0.527
CER, mg/d, median (IQR)	2297.7 (1872.9-3117.2)	1312.4 (1186.5-1459.6)	743.6 (551.5-892.7)	<0.001*
BMI, mean±SD (N=103)	25.2±3.8	24.9±3.6	21.8±2.8	<0.001*

* p < 0.05

Abbreviations: APACHE-II = Acute Physiology And. Chronic Health Evaluation II; BMI = body mass index; CER = creatinine excretion rate; eGFR = estimated glomerular filtration rate; IQR = interquartile range; NIHSS = National Institute of Health Stroke Scale; SD = standard deviation

Table 2. Patient profile according to outcome status.

Characteristics	Death or Dependence (mRS 3-6) at 6 Months			Death or Disability (mRS 2-6) at 6 Months		
	mRS 0-2 (N=31)	mRS 3-6 (N=125)	p Value	mRS 0-1 (N=20)	mRS 2-6 (N=136)	p Value
Age, y, mean±SD	65.7±12.2	68.5±13.5	0.291	64.1±13.5	68.5±13.2	0.170
Men, n (%)	19 (61.3)	77 (61.6)	0.975	12 (60.0)	84 (61.8)	0.880
Stroke subtype and clinical severity						
Ischemic Stroke, n (%)	19 (61.3)	64 (51.2)	0.314	12 (60.0)	71 (52.2)	0.514
Baseline NIHSS, median (IQR)	8 (3-15)	17 (12-22)	<0.001	7.5 (2.3-14.5)	16 (10.3-21)	<0.001
APACHE-II score, mean±SD	9.5±3.6	13.1±5.0	<0.001	9.0±3.1	12.8±5.0	0.001

Table 2. contd...

Characteristics	Death or Dependence (mRS 3-6) at 6 Months			Death or Disability (mRS 2-6) at 6 Months		
	mRS 0-2 (N=31)	mRS 3-6 (N=125)	p Value	mRS 0-1 (N=20)	mRS 2-6 (N=136)	p Value
Comorbidity, n (%)						
Prior Stroke	3 (9.7)	39 (31.2)	0.016	2 (10.0)	40 (29.4)	0.068
Hypertension	21 (67.7)	89 (71.2)	0.705	12 (60.0)	98 (72.1)	0.269
Diabetes	4 (12.9)	33 (26.4)	0.114	3 (15.0)	34 (25.0)	0.409
Atrial fibrillation	3 (9.7)	14 (11.2)	0.808	2 (10.0)	15 (11.0)	1.000
Physical and lab data at admission						
Systolic blood pressure, mmHg, mean±SD	177.8±28.8	177.5±37.6	0.966	183.4±29.7	176.7±36.8	0.445
Diastolic blood pressure, mmHg, mean±SD	97.0±15.4	98.3±23.5	0.778	101.0±14.0	97.6±23.1	0.519
Blood glucose, mg/dL, mean±SD	147.8±72.7	162.2±72.2	0.321	145.3±38.3	161.4±75.9	0.354
Albumin, mg/dL, mean±SD	4.0±0.8	3.6±0.6	0.008	4.1±1.0	3.6±0.6	0.011
eGFR, mL/min/1.73m ² , median (IQR)	65.6 (55.5-74.6)	56.6 (38.5-71.3)	0.031	63.6 (56.3-74.4)	57.0 (39.0-72.1)	0.075
BMI, mean±SD (N=103)	24.9±3.7	23.6±3.7	0.203	25.3±2.9	23.6±3.8	0.177

Abbreviations: APACHE-II = Acute Physiology And. Chronic Health Evaluation II; BMI = body mass index; CER = creatinine excretion rate; eGFR = estimated glomerular filtration rate; IQR = interquartile range; mRS = modified Rankin Scale; NIHSS = National Institute of Health Stroke Scale; SD = standard deviation

Table 3. Association of urinary creatinine excretion rate with 6-month outcome in critically-ill acute stroke patients by multivariate regression model*.

	OR	95% CI	P value
Death or dependence (mRS 3-6)			
Highest CER	1.00 (reference)		
Middle CER	2.24	0.73-6.92	0.160
Lowest CER	4.96	1.22-20.15	0.025
Death or disability (mRS 2-6)			
Highest CER	1.00 (reference)		
Middle CER	5.74	1.40-23.63	0.015
Lowest CER	5.00	1.02-24.46	0.047

*The multivariate model included classified CER, age, sex, baseline NIHSS score, APACHE-II score on admission, history of stroke, albumin and eGFR. Abbreviations: APACHE-II = Acute Physiology And. Chronic Health Evaluation II; CER = creatinine excretion rate; CI = confidence interval; eGFR = estimated glomerular filtration rate; mRS = modified Rankin Scale; OR = odds ratio

higher stroke mortality and long-term cardiovascular complications [9-11]. On the other hand, urinary CER is an established urine biomarker to assess total-body muscle mass, and it has advantages in cost-effectiveness, readily availability and accuracy [5]. Anthropometry is an alternative but it measures only individual muscle groups and is less accurate [5]. Computerized tomography to assess muscle mass is expansive and has to expose the patients in

radiation [5]. Dual-energy X-ray absorptiometry is also expansive and is possibly inaccurate in patients with altered body water content [12]. CER had been linked to higher cardiovascular risk and mortality in general population [6], and it also had been related to higher mortality in persons with chronic coronary artery disease [7], in renal transplant recipients [13] and in type 2 diabetics with nephropathy [14]. To our knowledge, this is the first study to report a link

between low CER and poor outcome in severe acute stroke patients.

The mechanisms underlying the association of CER with acute stroke outcomes may be multi-factorial. First of all, muscle is the primary target for insulin action and glucose disposal [15]. It has been reported that low muscle mass is associated with higher fasting glucose and insulin resistance even in non-diabetics, [16] and insulin resistance has been shown to be a predictor of cardiovascular and cerebrovascular diseases [17]. In addition, low muscle mass and insulin resistance were both related to low levels of insulin-like growth factor-1, which promotes glucose uptake by muscle and low levels of that is associated with poor stroke outcome [18, 19] Second, low muscle mass is an indicator of malnutrition. Malnutrition was reported in 8-34% of acute stroke patients on admission, [20] and several studies have demonstrated poor outcomes in terms of length of stay, complications, disability and death in malnourished compared to well-nourished acute stroke patients [21-24]. Moreover, some medium-sized studies had shown a benefit of protein-energy supplement on the reduction of poor outcome or death in malnourished acute stroke patients [25, 26]. Third, low muscle mass was associated with physical disability and decreased cardiopulmonary fitness in elderly. [27]. It had been reported that individuals with lower CER achieved lower metabolic equivalents and maximum heart rate after the exercise treadmill test, which may indicate poor physical fitness and cardiovascular function [7]. Physical inactivity had been recognized as an independent risk factor for stroke, (1) and pre-stroke physical activity was associated to a less severe stroke and better long-term outcome [28] There were also increasing evidences showing that stroke survivors may benefit from exercise training to improve the aerobic fitness and functional outcome [29, 30].

This study has limitations. First, BMI was not adjusted in our analysis because BMI was only available for some patients. Second, ischemic and hemorrhagic stroke were not further analyzed separately because of the modest sample size. Third, the study population comprised critically-ill stroke patients, who were in a stressful and metabolically demanding situation. In such a situation, the effect of muscle mass, which represents a metabolic reserve to deal with the demand, on the stroke outcome may be more prominent. Whether the predictive value of urine CER on stroke outcome still present in the patients with less severe strokes need further evaluation. Fourth, our cohort included only Asian patients and the generalizability of the findings to other races is unknown. Finally, the CER data in our study was calculated by creatinine in morning spot urine multiply 24-hour urine volume, not measured by the creatinine from 24-hour urine collection. Although there have been studies showing that there was good correlation between proteinuria measured by spot urine and 24-hour urine [31], the correlation between CER measured by spot urine and 24-hour urine still need to be evaluated.

In conclusion, we observed that low baseline CER, a marker of muscle mass, was independently associated with poor 6-month outcome among critically ill acute stroke patients. Future studies will need to focus on stroke patients of all levels of severity, assess any differences by stroke type, and include non-Asian patients as well. Furthermore,

the possible mechanisms behind the association between low CER and poor stroke outcome need to be investigated. Given that CER might be a potentially modifiable risk factor, future studies could also examine whether pre-morbid modification of this risk factor, potentially through exercise or protein-energy supplement, could be helpful for improving acute stroke outcomes.

ETHICAL STATEMENT

Work was the reported experiments in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2008 (<http://www.wma.net/en/20activities/10ethics/10helsinki/>).

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

This paper is supported by Chang Gung Medical Research Project Grant (CMRPG 660311), Taiwan.

REFERENCES

- [1] Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, *et al.* Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke; J Cerebr Circ* 2011;42(2):517-84.
- [2] Ovbiagele B, Bath PM, Cotton D, Vinisko R, Diener HC. Obesity and recurrent vascular risk after a recent ischemic stroke. *Stroke; a journal of cerebral circulation.* 2011; 42(12): 3397-402.
- [3] Katsnelson M, Rundek T. Obesity paradox and stroke: noticing the (fat) man behind the curtain. *Stroke; J Cerebr Circ* 2011; 42(12): 3331-2.
- [4] Scherbakov N, Dirnagl U, Doehner W. Body weight after stroke: lessons from the obesity paradox. *Stroke; J Cerebr Circ* 2011; 42(12): 3646-50.
- [5] Heymsfield SB, Arteaga C, McManus C, Smith J, Moffitt S. Measurement of muscle mass in humans: validity of the 24-hour urinary creatinine method. *Am J Clin Nutr* 1983;37(3):478-94.
- [6] Oterdoom LH, Gansevoort RT, Schouten JP, de Jong PE, Gans RO, Bakker SJ. Urinary creatinine excretion, an indirect measure of muscle mass, is an independent predictor of cardiovascular disease and mortality in the general population. *Atherosclerosis.* 2009; 207(2): 534-40.
- [7] Ix JH, de Boer IH, Wassel CL, Criqui MH, Shlipak MG, Whooley MA. Urinary creatinine excretion rate and mortality in persons with coronary artery disease: the Heart and Soul Study. *Circulation.* 2010; 121(11): 1295-303.
- [8] Horio M, Imai E, Yasuda Y, Watanabe T, Matsuo S. Modification of the CKD epidemiology collaboration (CKD-EPI) equation for Japanese: accuracy and use for population estimates. *Am J Kidney Dis.* 2010; 56(1): 32-8.
- [9] Schutte R, Schmieder RE, Huisman HW, Smith W, van Rooyen JM, Fourie CM, *et al.* Urinary albumin excretion from spot urine samples predict all-cause and stroke mortality in Africans. *American journal of hypertension.* 2014; 27(6): 811-8.
- [10] Tofik R, Ekelund U, Torffvit O, Sward P, Rippe B, Bakoush O. Increased urinary IgM excretion in patients with chest pain due to coronary artery disease. *BMC cardiovascular disorders.* 2013; 13: 72.
- [11] Huang YC, Wu YL, Lee MH, Lee JD, Wu CY, Hsu HL, *et al.* Association of renal biomarkers with 3-month and 1-year outcomes

- among critically ill acute stroke patients. *PLoS one*. 2013;8(9):e72971.
- [12] Proctor DN, O'Brien PC, Atkinson EJ, Nair KS. Comparison of techniques to estimate total body skeletal muscle mass in people of different age groups. *Am J Physiol* 1999;277(3 Pt 1):E489-95.
- [13] Oterdoom LH, van Ree RM, de Vries AP, Gansevoort RT, Schouten JP, van Son WJ, *et al*. Urinary creatinine excretion reflecting muscle mass is a predictor of mortality and graft loss in renal transplant recipients. *Transplantation*. 2008; 86(3): 391-8.
- [14] Sinkeler SJ, Kwakernaak AJ, Bakker SJ, Shahinfar S, Esmatjes E, de Zeeuw D, *et al*. Creatinine excretion rate and mortality in type 2 diabetes and nephropathy. *Diabetes care*. 2013; 36(6):1489-94.
- [15] Khamseh ME, Malek M, Aghili R, Emami Z. Sarcopenia and diabetes: pathogenesis and consequences. *Br J Diab Vasc Dis* 2011; 11(5): 230-4.
- [16] Kalyani RR, Metter EJ, Ramachandran R, Chia CW, Saudek CD, Ferrucci L. Glucose and insulin measurements from the oral glucose tolerance test and relationship to muscle mass. *J Gerontol Series A. Biol Sci Med Sci* 2012; 67(1):74-81.
- [17] Facchini FS, Hua N, Abbasi F, Reaven GM. Insulin resistance as a predictor of age-related diseases. *J Clin Endocrinol Metab*. 2001; 86(8): 3574-8.
- [18] Denti L, Annoni V, Cattadori E, Salvagnini MA, Visioli S, Merli MF, *et al*. Insulin-like growth factor 1 as a predictor of ischemic stroke outcome in the elderly. *Am J Med* 2004; 117(5): 312-7.
- [19] Clemmons DR. Role of insulin-like growth factor in maintaining normal glucose homeostasis. *Hormone Res* 2004;62 Suppl 1:77-82.
- [20] Dennis M. Nutrition after stroke. *Br Med Bull* 2000; 56(2): 466-75.
- [21] Yoo SH, Kim JS, Kwon SU, Yun SC, Koh JY, Kang DW. Undernutrition as a predictor of poor clinical outcomes in acute ischemic stroke patients. *Arch Neurol* 2008;65(1):39-43.
- [22] Martineau J, Bauer JD, Isenring E, Cohen S. Malnutrition determined by the patient-generated subjective global assessment is associated with poor outcomes in acute stroke patients. *Clin Nutr* 2005;24(6):1073-7.
- [23] Poor nutritional status on admission predicts poor outcomes after stroke: observational data from the FOOD trial. *Stroke; J Cereb Circ* 2003; 34(6): 1450-6.
- [24] Finestone HM, Greene-Finestone LS, Wilson ES, Teasell RW. Prolonged length of stay and reduced functional improvement rate in malnourished stroke rehabilitation patients. *Arch Phys Med Rehabil* 1996;77(4):340-5.
- [25] Ha L, Hauge T, Spenning AB, Iversen PO. Individual, nutritional support prevents undernutrition, increases muscle strength and improves QoL among elderly at nutritional risk hospitalized for acute stroke: a randomized, controlled trial. *Clin Nutr* 2010;29(5):567-73.
- [26] Gariballa SE, Parker SG, Taub N, Castleden CM. A randomized, controlled, a single-blind trial of nutritional supplementation after acute stroke. *JPEN J Parenter Enter Nutr* 1998;22(5):315-9.
- [27] Chien MY, Kuo HK, Wu YT. Sarcopenia, cardiopulmonary fitness, and physical disability in community-dwelling elderly people. *Phys Ther* 2010; 90(9): 1277-87.
- [28] Krarup LH, Truelsen T, Gluud C, Andersen G, Zeng X, Korv J, *et al*. Prestroke physical activity is associated with severity and long-term outcome from first-ever stroke. *Neurol* 2008; 71(17): 1313-8.
- [29] Gordon NF, Gulanick M, Costa F, Fletcher G, Franklin BA, Roth EJ, *et al*. Physical activity and exercise recommendations for stroke survivors: an American Heart Association scientific statement from the Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention; the Council on Cardiovascular Nursing; the Council on Nutrition, Physical Activity, and Metabolism; and the Stroke Council. *Circulation*. 2004; 109(16): 2031-41.
- [30] Stoller O, de Bruin ED, Knols RH, Hunt KJ. Effects of cardiovascular exercise early after stroke: systematic review and meta-analysis. *BMC Neurol* 2012;12:45.
- [31] Siu WK, Mak CM, Lee HCH, Tam S, Lee J, Chan TM, *et al*. Correlation study between spot urine protein-to-creatinine ratio and 24-hour urine protein measurement in 174 patients for proteinuria assessment. *Hong Kong J Nephrol* 2011;13(2):51-4.