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The relationship between musekna index and stroke severity in patients with acute ischemic stroke

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ABSTRACT

Acute stroke is an important cause of morbidity and mortality. Prediction tools are especially helpful in this situation in guiding for medical treatment decision. It is found that prognostic index is predictor of mortality and heart failure in patients with ischemic heart failure implanted with an ICD, the prognostic index (PI) being built according to the formula: 120 - age + mean 24 h systolic blood pressure - (creatinine * 10). However, a mean 24 h systolic blood pressure calculation is not clinically easy. Therefore, we propose a new modified prognostic index (Musekna Index). Musekna Index (MI) was calculated as "120 - age + mean arterial pressure - (creatinine * 10)". In this study, we aimed to investigate the relationship between MI and stroke severity in patients with acute ischemic stroke. This cross-sectional study included 162 patients (males, 64; females, 98; 67 ± 15 years) with acute ischemic stroke. Patients were divided into two groups based on the calculated National Institutes of Health Stroke Scale (NIHSS) score (Group 1, NIHSS score < 16; Group 2, NIHSS score ≥ 16). Demographic, clinical, and laboratory data for all patients were collected. Musekna Index (Modified Prognostic Index) was calculated as "120 - age + mean arterial pressure - (creatinine * 10)". MI index was calculated admission to the neurology care unit. Echocardiographic examinations were performed using the parasternal longitudinal axis and apical 4-chamber windows in accordance with the recommendations of the American Echocardiography Committee. There were no significant differences among the demographic parameters of patients. MI was significantly higher in Group 1 patients than in Group 2 patients (139±15.6 vs 132±13.7, p=0.028). Our results suggest that MI is associated with stroke severity on admission in patients with acute ischemic stroke.

1. Introduction

Acute stroke is an important cause of morbidity and mortality. Accurate estimation of stroke prognosis is important for several reasons. First, it may guide treatment decisions and utility clinical management. Also, it may help health care supplier communicate effectively with patients and their families and to plan the long-term living setting (Ntaios et al., 2012; Sung et al., 2014). Outcomes following a stroke event can range from full recovery, through varying degrees of disability to death (Drozdowska et al., 2019). Accurate and early prediction of survival in patients with acute

stroke is important (Kwok et al., 2013). Several factors are known to affect the short-term prognosis in acute cerebrovascular disease (CVD). There are several prediction models for acute CVD (Fullerton et al., 1988; Rodrigues and Joshi, 1991). But, these prediction models are complex and not proper for common use. Therefore, a prognostic model needs to be easily applicable in the clinical setting and does not require sophisticated calculations (Muscari et al., 2011).

This study aimed to create a simple and practical index that can be systematically and consistently applied in routine clinical practice and to investigate the relationship between Musekna Index (MI) and stroke severity in patients with acute ischemic stroke.

2. Materials and methods

Patient selection

This cross-sectional study included 162 patients (males, 64; females, 98; 67 ± 15 years, range 41- 92 years) with acute ischemic stroke (≤24 hours of symptom onset) admitted to the neurology care unit, between October 2016 and December 2018. Twenty four patients were excluded. Demographic and baseline clinical data, including neurological deficit severity assessment with NIHSS on admission to the neurology care unit were recorded. Patient clinical data, history of cardiovascular risk factors and stroke onset were determined, and neurologic examination was conducted at the time of admission. The diagnosis was made based on the neurologic examination and cranial imaging within 24 hours of symptom onset. Patients with a well-defined time of ischemic stroke symptom onset were included in the study and those with any previous history of cerebrovascular disease or transient ischemic attack, cerebral hemorrhage, documented atrial fibrillation, coronary heart disease, congestive heart failure, serious valvular heart disease, congenital heart disease, chronic obstructive pulmonary disease, chronic renal failure were excluded. Twenty four patients were excluded because of the previous history of cerebrovascular disease (n=5), documented atrial fibrillation (n=6), congestive heart failure (n=4), coronary heart disease (n=5), serious valvular heart disease (n= 4). Baseline stroke severity was assessed using the NIHSS score (Lyden, 2017).

All patients underwent immediate computed tomography after admission to the emergency department. Troponin levels were measured and electrocardiogram (ECG) was recorded after admission to the neurology care unit. Echocardiography was performed within the first 48 hours of admission to the neurology care unit. The NIHSS evaluation and echocardiographic examination were conducted by blinded investigators. The study was approved by the Ethics Committee of our hospital, and informed consent was obtained. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Definition of stroke and assesment of stroke severity

According to the updated definition of stroke in the American Heart Association/American Stroke Association guidelines, ischemic stroke is diagnosed based on the combination of symptoms and/or signs of typical neurological dysfunction and imaging evidence of central nervous system infarction. Therefore, ischemic stroke is defined as a neurological dysfunction episode caused by focal cerebral, spinal, or retinal infarction on imaging (Sacco et al., 2013).

NIHSS is a simple, valid, and reliable systematic assessment tool that measures acute stroke-related neurologic deficit (Lyden, 2017). The NIHSS score is very important to scale for clinical assessment as it enables the determination of appropriate treatment, prediction of lesion size, measurement of stroke severity, and prediction of patient outcome in patients with acute ischemic stroke. The NIHSS comprises 11 different elements evaluating specific ability. Each ability is scored between 0 and 4, where 0 corresponds to normal functioning and 4 corresponds to complete impairment. A patient's NIHSS score is calculated by adding the score for each element of the scale; 42 is the highest score possible. A higher NIHSS score corresponds to greater impairment of cerebral function in a stroke patient.

The higher the NIHSS score, the higher the impairment of a stroke patient. According to NIHSS score, there are five-stroke severity groups: NIHSS =0 (no stroke), NIHSS=1-4 (minor stroke), NIHSS=5-15 (moderate stroke), NIHSS=16-20 (moderate to severe stroke), NIHSS=21-42 (severe stroke). A baseline NIHSS score greater than 16 indicates a strong probability of patient disability and death (Lyden, 2017).

Stroke severity at admission to the neurology care unit was assessed by the NIHSS score by a neurologist (U.O). Patients were categorized into two groups; Group 1 comprised of patients with non-severe stroke (NIHSS<16; n=58), whereas Group 2 comprised of patients with severe stroke (NIHSS≥16; n=22).

Cerebral infarct volume measurements

A neurologist calculated the "cerebral infarct volume" in each patient by using Analyze 12.0, a software package for biomedical image analysis (Biomedical Imaging Resource, New York, NY, USA). The area of interest were segmented using the Region Grow in the Volume Edit module, with manual elimination of artifacts when essential. The total infarct volume was calculated as mL.

Musekna index (Modified prognostic index)

Antonini et al. found that prognostic index was predictor of mortality and heart failure in patients with ischemic heart failure implanted with an ICD (Antonini

et al., 2015). The prognostic index (PI) was calculated according to the formula: 120 - age + mean 24 h systolic blood pressure - (creatinine * 10). However, a mean 24 h systolic blood pressure calculation is not clinically easy. Also, in a recent analysis of the Medical Research Council Mild Hypertension Trial, sphygmomanometric PP was a predictor of cardiovascular events and MAP was a better predictor of acute stroke than PP (Millar et al., 1999). A study of 24-hour BP monitoring also ensured evidence that PP is the important predictor of cardiovascular events; MAP is the major independent predictor of acute cerebrovascular events (Verdecchia et al., 2001; Zheng et al., 2008). Therefore, we propose a new modified prognostic index (MI) in patients with acute ischemic stroke. MI was calculated as "120 - age + mean arterial pressure - (creatinine * 10)"

Statistical analysis

Statistical analysis was conducted with the SPSS statistical package (Version 12.0; SPSS Inc., Chicago, IL,USA). All baseline parameters were analyzed. Continuous variables are expressed as mean±SD, and categorical variables are expressed as percentages. Intra-observer variability was calculated as the absolute difference between the two measurements as a percentage of their mean. Student t-test and Chi-square test were used for comparison of data as appropriate. p values <0.05 were considered statistically significant. The Pearson's or Spearman's correlation was used for assessing correlations between variables. Multivariate analyses were performed.

3. Results

Baseline characteristics

The baseline characteristics of patients are summarized in (Table 1). Clinical characteristics of groups were similar with respect to gender, hypertension, diabetes, smoking (p>0.05). Age, systolic blood pressure (BP), diastolic BP, mean arterial pressure, heart rate, dyslipidemia, infarct volume, troponin, glucose, HbA1c, creatinine, LDL cholesterol levels in Group 2 patients were significantly higher than Group 1 patients (p<0.05). MI was significantly higher in Group 1 patients than Group 2 patients (p<0.05).

Echocardiographic findings

Echocardiographic parameters are summarized in Table 2. LV wall thickness and E/e' values were significantly higher in Group 2 patients than in Group 1 patients (p < 0.05). LVEF was significantly higher in Group 1 patients having lower NIHSS scores than in Group 2 patients having higher NIHSS scores.

Electrocardiographic findings

Group 2 patients showed significantly longer QTc, QTd, QTcd than Group 1 patients (Table 2). Correlation analysis performed to investigate the relationship between NIHSS score and clinical parameters showed a negative correlation among the NIHSS score and MI and LVEF. Also, there was a positive correlation between the NIHSS score and age, heart rate and E/e' (Table 3). Logistic regression analysis was performed

Table 1. Clinical characteristics of patients.

Variables	Group 1 (NIHSS score<16) n=97	Group 2 (NIHSS score≥16) n=41	p Value
Age (years)	64.8 ± 13.9	71.5±16.9	0.038
Gender (F/M), n	56 / 41	26 / 15	0.671
Hypertension, n %	45 (46 %)	23 (56%)	0.070
SBP (mmHg)	141.9±16.7	158.6±17.3	0.039
DBP (mmHg)	74.2±9.4	88.1±13.5	0.042
MAP (mmHG)	94.7±10.1	105.3±13.4	0.029
Heart Rate (bpm)	91.8±13.5	117±13.4	0.024
Musekna Index	139±15.6	132±13.7	0.028
Diabetes Mellitus, n %	28 (28%)	13 (32%)	0.075
Smoking, n %	13 (14%)	7 (18%)	0.083
Dyslipidemia, n %	13 (14%)	15 (38%)	0.040
Infarct volume (mL)	17 mL ± 2.5	46 mL ± 4.5	0.032
Troponin (ng/L)	7.432	16.953	0.034
HbA1c (%)	6.78±1.32	8.68±1.92	0.023
Glucose (mg/dl)	139.7±35.8	197.2±47.8	0.037
Creatinine (mg/dL)	1.3±0.5	2.1±0.7	0.025
LDL cholesterol (mg/dL)	106.1±25.6	134.2±38.9	0.007
HDL cholesterol (mg/dL)	40.5±11.4	38.2±9.3	0.547

*F:Female, † M:Male, ‡ SBP: Systolic Blood Pressure, § DBP: Diastolic Blood Pressure, ‖ MAP: Mean Arterial Pressure, ¶ LDL: Low Density Lipoprotein, ** HDL: High Density Lipoprotein.

Table 2. Echocardiographic and electrocardiographic parameters of patients.

Variables	Group 1 (NIHSS score<16) n=97	Group 2 (NIHSS score≥16) n=41	p Value
LV septal thickness, mm	11.1±1.7	12.9±1.9	0.032
LVDd (mm)	50.4±5.7	54.4±6.4	0.413
LV posterior Wall thickness, mm	10.6±1.3	12.1±1.7	0.027
LVDs (mm)	41.3±4.6	43.7±4.9	0.325
LVEDV (mL)	87.0±15.1	94.6±23.9	0.219
LVESV (mL)	42.3±11.7	45.2±13.8	0.426
LAD (mm)	39.7±5.2	43.1±5.2	0.572
RAD (mm)	31.3±3.7	34.9±3.4	0.492
RVDd (mm)	29.3±2.7	31.4 ± 2.5	0.371
LVEF (%)	58.6±6.3	52.7±7.1	0.027
E/e'	8.4±3.2	11.5 ±3.4	0.030
QTc (ms)	463±47.7	536±62.3	0.040
QTd (ms)	56.1±4.6	89.2±4.8	0.033
QTcd (ms)	60.7±3.4	89.5±4.3	0.044

NIHSS: National Institutes of Health Stroke Scale, † LV: Left Ventricle, ‡ LVDd: Left ventricular diastolic diameter, § LVDs: Left ventricular systolic diameter, ‖ LVEDV: Left ventricular end-diastolic volume, ¶ LVESV: Left ventricular end-systolic volume, ** LAD: Left atrial diameter, †† RAD: Right atrial diameter, ‡‡ RVDd: Right ventricular diastolic diameter, §§ LVEF: Left ventricular ejection fraction, ||| QTc: corrected QT interval, ¶¶ QTcd: QTc dispersion, *** QTd: QT dispersion.

to identify the potential predictors for stroke severity. Results of the multivariate analysis revealed MI, age, LV EF, and heart rate powerful predictor of severe ischemic stroke (Table 4).

Table 3. Correlation between NIHSS score and clinical parameters in patients with acute ischemic stroke.

Parameters	Pearson's correlation coefficient (r value)	p Value
Musekna Index	-0.656	0.023
LVEF	-0.432	0.032
E/e'	0.312	0.041
Age	0.480	0.039
Heart rate	0.380	0.03

* NIHSS: National Institutes of Health Stroke Scale, † LVEF: Left ventricular ejection fraction.

Table 4. Multivariate logistic regression analysis between NIHSS score and clinical parameters in patients with acute ischemic stroke.

Parameters	OR	95 % CI	p Value
Parameters	OR	95 % CI	p Value
Musekna Index	0.562	0.483-0.840	0.017
LVEF	0.725	0.687-0.785	0.029
Age	1.324	1.053-1.435	0.036
Heart rate	1.090	0.867-1.191	0.527

NIHSS: National Institutes of Health Stroke Scale, † LVEF: Left ventricular ejection fraction.

4. Discussion

Acute stroke is characterized by severe autonomic dysfunction, including alterations in the autonomic reflex pathways, central autonomic neuroanatomical sites, and hormonal factors. Stroke-related sympathetic activation is high in patients with higher NIHSS score. Irrespective of prior cardiovascular status, an acute stage of stroke importantly influences systemic BP, heart rate, LV function, and biochemical parameters (Ripoll et al., 2018).

Predicting morbidity and mortality in the acute cerebrovascular disease remains a challenge in clinical practice and continues to encourage researchers to develop new and more accurate prognostic tools (Racosta et al., 2014). Several studies have developed simplified prognostic model systems. However, there has been no published simple prognostic scoring for early period acute ischemic stroke mortality. The Guy's score and Fiorellis' prediction model were developed to predict two and four month outcome (Allen, 1984; Fiorelli et al., 1995). Gompertz's G-score (simplified Guy's score) and Fullerton's prognostic index were used to predict the mortality at six months (Fullerton et al., 1988; Gompertz et al., 1994). Wade et al. developed his prognostic scoring system for prediction of outcome over a 2-year period (Wade et al., 1984). All the prognostic scoring systems are complex and do not lend themselves to bedside use.

We have developed a new prognostic scoring system (MI) for patients with acute ischemic stroke during the early hospitalisation period. MI is built with three easily measured clinical predictors on which data were routinely available for all acute stroke patients. In this study, we found that MI was significantly lower in patients who have a severe stroke. MAP is a function of left ventricular contractility, heart rate, and systemic arterial resistance and aortic elasticity (Benetos et al., 1997). In this study, elevated MAP level was independently associated with acute ischemic stroke severity, which was similar to other clinical studies (Mazza et al., 2001; Verdecchia et al., 2001). Soliman et al. found that stroke disability was higher in a patient with advanced age. Mortality associated with stroke increases with age (Soliman et al., 2018). Mathisen et al. found that long-term mortality was associated with elevated values of creatinine at the time of the acute stroke (Mathisen et al., 2016). In the present study, we found that admission creatinine values were significantly higher in severe stroke patients. Mostofsky et al. suggesting that clinical risk factors for cardiovascular diseases including age, diabetes mellitus, hypertension may indicate vascular pathogenesis resulting from reduced renal clearance. Renal function predicts survival in patients with acute ischemic stroke (Mostofsky et al., 2009).

The effect of ischemic stroke severity on the LV function is not very well known, and only a few studies are investigating this relationship (Milionis et al., 2013; Kim et al., 2016). Sung et al. found that severe acute ischemic stroke patients had lower LVEF (Sung et al., 2019). In our study, we found that LVEF was significantly higher in patients with lower NIHSS scores than in those with higher NIHSS scores. Also, infarct volume was significantly higher in Group 2 patients than Group 1 patients.

Previous studies have reported that a relationship between acute cerebrovascular disease and QT (Lederman et al., 2014; Lederman et al., 2019). Lazar et al. found that a positive relationship between baseline QTd and NIHSS and modified ranking scores (Lazar et al., 2008). In our study, we found that QT parameters were significantly higher in Group 2 patients than Group 1 patients.

Hypertension, hyperlipidemia and diabetes mellitus are important risk factors for atherosclerotic cerebrovascular disease (Wu et al., 2010). We found that blood pressure at admission is significantly higher in severe ischemic stroke patients. Li et al. suggested that the NIHSS score on admission in the H-type hypertension group was significantly higher than that in the control group (Li et al., 2018). However, Bonardo et al. found that, large infarct volume was not

associated with high blood pressure at admission in young patients with acute ischemic stroke (Bonardo et al., 2018). In our study, we found that LDL cholesterol was significantly higher in patients with higher NIHSS scores than in those with lower NIHSS scores.

In this study, we found that troponin levels were significantly higher in severe ischemic stroke patients. Chang et al. showed that cardiac biomarkers are related with acute large vessel occlusion in patients with ischemic stroke (Chang et al., 2019). Hendrix et al. found that diabetes mellitus history is an important predictor of stroke severity (Hendrix et al., 2019). Lindsberg and Roine observed that increasing blood glucose level is common in the early phase of acute stroke (Lindsberg and Roine, 2004) . In our study blood glucose and HbA1c levels were significantly higher in severe stroke patients on admission. Although up to one-third of severe acute ischemic stroke patients have diagnosed diabetes, probably a major proportion of patients have stres induced hyperglycemia mediated partly by the release of cortisol and norepinephrine (Lindsberg and Roine, 2004). Bogdanovic et al. found that acute hyperglycemia in asymptomatic diabetic patients have significant negative effects on LV function (Bogdanovic et al., 2019). In our study, we found that E/é value was significantly higher in severe stroke patients. Ryu et al. suggested that E/e' ratios were associated with arterial occlusion in AF-related acute ischemic stroke and may play an important role in identifying patients at high risk of severe stroke (Ryu et al., 2018).

In conclusion, we have developed the MI a simple score for assessing ischemic stroke severity and prognosis based on signs and symptoms noted upon admission. The modified prognostic index score is not intended to replace any of the currently used prognostic scoring systems. Our purpose is providing physicians not trained in the use of more sophisticated scales with a readily available clinical parameters to be used for clinical purposes. It is also intended to be used when clinical, laboratory, or neuroimaging data needed for other scores, are not fully available. However, it would be preferable for our prognostic index to be tested in the other independent samples and in prospective studies.

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