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The effectiveness of serum S100B, TRAIL and adropin levels in predicting clinical outcome, final infarct core and stroke subtypes of acute ischemic stroke patients

S100B, TRAIL and Adropin predicting stroke prognosis

Eficacia de los niveles séricos de S100B, TRAIL y adropina para predecir el resultado clínico, el núcleo del infarto final y los subtipos de ataque cerebrovascular de los pacientes con accidente cerebrovascular isquémico agudo

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Contribution of each author:

Ozge Altintas Kadirhan: developed the theoretical formalism, performed the analytic calculations.

Okkes Taha Kucukdagli and Bedia Gulen: performed the research and collected the data in Emergency Department.

Bedia Gulen: supervised the project.

All authors discussed the results and contributed to the final manuscript.

Introduction: To include

Objectives: To identify the significance of TRAIL and adropin release and the relative changes related to S100B levels and the relationship between these biomarkers with final infarct core, clinical outcome, and the presence of large artery atherosclerosis in acute stroke patients.

Material and methods: Over a one-year period, demographic, clinical, and neuroimaging findings of 90 consecutive patients with acute ischemic stroke were evaluated.

Results: Among our study population, the mean age was 69.28 ± 10 and 39 patients were female. The increased level of S100B and the decreased levels of sTRAIL with adropin were significantly associated with the moderate to the severe patient neurologic presentation (p=.0001, p=.002, p =.002, respectively). On control CT, a large infarct core was significantly associated with decreased serum level of sTRAIL and adropin (p=.001 and p=.000; respectively); however, the levels of S100B were not significantly associated with good ASPECT score (p=.684). Disability and unfavorable outcome were significantly related to the decreased level of sTRAIL and adropin (p=.001 and p=.000; respectively for THRIVE score>5). Decreased sTRAIL and adropin levels and increased S100B level were correlated with the presence of large artery atherosclerotic etiologic factor among the study population (p=.000, p=.000, p =.036, respectively).

Conclusion: TRAIL and Adropin serum levels are associated with poor clinical outcome and greater infarcted area in acute ischemic stroke patients.

Key words: TNF-related apoptosis-inducing ligand; infarction, posterior cerebral artery; stroke;

Introducción. Incluir

Objetivo. Identificar la importancia de la liberación de TRAIL y adropin y los cambios relativos relacionados con los niveles de S100B y la relación entre estos biomarcadores con el núcleo final del infarto, el resultado clínico y la presencia de aterosclerosis de arterias grandes en pacientes con ataque cerebrovascular agudo.

Materiales y métodos. Durante un período de un año, se evaluaron los hallazgos demográficos, clínicos y de neuroimagen de 90 pacientes consecutivos con ataque cerebrovascular isquémico agudo.

Resultados. Entre la población de nuestro estudio, la edad media fue de 69,28 ± 10 y 39 pacientes eran mujeres. El aumento del nivel de S100B y la disminución de los niveles de sTRAIL con adropina se asociaron significativamente con la presentación neurológica del paciente de moderada a grave (p = ,0001, p = ,002, p = ,002, respectivamente). En la TC de control, un gran núcleo de infarto se asoció significativamente con una disminución del nivel sérico de sTRAIL y adropina (p = ,001 y p = ,000; respectivamente); sin embargo, los niveles de S100B no se asociaron significativamente con una buena puntuación ASPECT (p = ,684). La discapacidad y el resultado desfavorable se relacionaron significativamente con la disminución del nivel de sTRAIL y adropina (p = ,001 yp = ,000; respectivamente para la puntuación THRIVE> 5). La disminución de los niveles de sTRAIL y adropina y el aumento del nivel de S100B se correlacionaron con la presencia de un factor etiológico aterosclerótico de arterias grandes entre la población de estudio (p = ,000, p = ,000, p = ,036, respectivamente).

Conclusiones. Los niveles séricos de TRAIL y Adropin se asocian con un resultado clínico deficiente y una mayor área infartada en pacientes con ataque cerebrovascular isquémico agudo.

Palabras clave: ligando inductor de apoptosis relacionado con TNF; infarto de la arteria cerebral posterior; accidente cerebrovascular

More than half of all deaths and disabilities in worldwide were caused by stroke (1,2). Extracranial and intracranial large artery atherosclerosis (LAA) is identified as a high etiologic risk factor because of accounts for 20 % of ischemic stroke (2,3). Diabetes is an independent risk factor for stroke via involving in the atherosclerotic process (4). The recent research has shown that increased blood glucose levels were associated with large ischemic core volume and poor clinical prognosis post-stroke (5).

Dysfunctional endothelium contributes to atherosclerosis initiation and progression (3,6). Tumor necrosis factor (TNF)-related apoptosis- inducing ligand (TRAIL) is a member of the TNF superfamily that activates the apoptotic pathways behind cell damage and disease progression (7). Recent studies have shown that TRAIL might contribute to stabilize atherosclerotic lesions, to ameliorate endothelial dysfunction by increasing the release of nitric oxide (8). Adropin is a recently identified regulatory protein at the potential biological mechanism of insulin sensitivity and endothelial function (9). The previous study that the patients with acute myocardial infarction were participated, was determined that the angiographic severity of coronary atherosclerosis is closely related to low adropin levels (10).

S100B is a useful “acute-phase” neurobiochemical known marker of brain damage and is closely associated with plaque instability and oxidative stress in stroke patients (11). Based on these findings, we aim to firstly investigate the significance of TRAIL and Adropin release and the relative changes related to S100B levels in acute stroke patients, and secondly analyze the association between these biomarkers with final infarct core, clinical outcome and the presence of large artery atherosclerosis combined with neuroimaging

and clinical risk assessment tools in acute stroke patients.

Material-and method

This prospective observational study was conducted at the emergency room (ER) and neurology department over a one-year period. We prospectively studied ninety ischemic stroke patients (patients with ischemic infarct) who admitted to emergency department in the first 24 h after symptom onset. Detailed data were registered prospectively for each patient including demographics, vascular risk factors, admission glucose level, and admission blood pressure levels.

A noncontrast computed tomography (CT) brain scan was performed to rule out hemorrhagic stroke on admission. On baseline and 24th hours control CT, we evaluated the Alberta Stroke Program Early computed tomography Score (ASPECTS). Early ischemic changes in the middle cerebral artery territory were quantified by the ASPECT scoring system, with a score of 10 indicating normal and -1 point for each infarcted region (12). Patients with ASPECT score 6-10 were classified as having a small infarct core in the study according to previous research (13). All patients underwent carotid duplex ultrasonography and magnetic resonance angiography due to diagnosed extracranial and intracranial atherothrombosis.

Large artery atherosclerosis is defined according to the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) classification system (14). Carotid doppler ultrasonography and brain imaging methods were used to determine accurately the etiological risk factor. Significant stenosis is defined as 50% and above the reduction in diameter the degree of internal cerebral artery or cerebral artery luminal diameter stenosis or occlusion in stroke patients,

presumably due to atherosclerosis (14).

The National Institutes of Health Stroke Scale (NIHSS) score was calculated for each patient on admission. The modified Rankin Scale (mRS) was recorded on admission, the first month, and the third month. Patients with mRS 0-2 were classified as having good neurologic outcome. Totaled Health Risks In Vascular Events (THRIVE)score was calculated for each patient at admission. THRIVE score is calculated total health risk in vascular events due to scoring the presence of hypertension, diabetes and atrial fibrillation, baseline NIHSS score and patient age. A THRIVE score of 0 to 5 was defined as good clinical recovery and prognosis as previously stated (15).

After the admission to the ER, blood sampling was performed from each patient to evaluate the study biomarkers. The results were recorded in pg/L for sTRAIL and S100B and ng/ml for adropin after analyzing the samples according to the protocol of the kit by using the sandwich enzyme immunoassay method (S100B Elisa Kit: Cat No: E 3039 Bioassay Technology Laboratory Co., Ltd., China; sTRAIL Elisa Kit: Cat No: E 1824 Bioassay Technology Laboratory Co., Ltd., China; Adropin Elisa Kit: Cat No: 201 12 3107 Sunred Technology Laboratory Co., Ltd., China).

All statistical analyses were performed using IBM SPSS Statistics 20 (USA) and the Microsoft Office Excel software. Comparative analyses between the study biomarkers and initial mRS, third month mRS, initial NIHSS, initial and control ASPECTS, initial THRIVE, the presence of LAA were performed using Chi-square test ($\chi 2$ test), independent samples t-test or Mann–Whitney U-test. When expected frequency is five or less then five, we used the Fischer's exact test. Age and test values were all expressed as means ± standard

deviations (SD). For all tests, a two-tailed P value < 0.05 was considered to indicate statistical significance with confidence intervals (CI) of 95%. A receiver operating characteristic (ROC) curve was constructed to determine the area under the curve (AUC), sensitivity, and specificity of the levels of study biomarker for the prediction of outcome in the study patients.

Ethics Statement: In the study, Research Ethics Committee at Bezmialem Vakif University approved all described procedures (Decision No: 11/30 June 03/2015).

Results

Among study population, the mean age was 69.28±10 and 39 patients were female (43.3 %). The leading vascular risk factor was hypertension (71.1 %). The baseline characteristics of the study patients are shown in table 1.

Upon admission to the ER, the patients had a mean NIHSS score of 17.08±4.65 points. 84 of 90 stroke patients had moderate to severe stroke with a NIHSS score higher than 10. At admission after the stroke onset, favorable mRS score of 0-2 was found in 7.8 % among study patients (n=7; 7.8 %). A significant proportion of patients completely recovered with a slight or no long-term disability. At third month, 51 (56.7%) patients had favorable neurologic outcome with a mRS score 0-2. Two patients died in the second month after discharge. 74 (82.2 %) patients had good clinical recovery after stroke with initial THRIVE score 0 to 5. Distribution of baseline and follow-up clinical scores to measure good clinical outcome and small infarct core in the study patients are demonstrated in figure 1.

Among stroke subtypes by TOAST classification, 24 (26.7%) patients had large artery atherosclerosis. Two patients with internal carotid artery (ICA)

occlusion, seven patients with middle cerebral artery (MCA) M1 segment occlusion and five patients with unilateral ICA stenosis, eight patients with unilateral MCA M1 segment stenosis were observed. Indeed, only two patients had bilaterally ICA stenosis. There was not any case as considered tandem occlusion.

22 study patients had large infarct burden (ASPECTS <6) on control cranial CT scans. We did not determine any hemorrhagic transformation on control neuroscans.

Among study biomarkers, the increased level of S100B and the decreased levels of sTRAIL with adropin were significantly associated with the moderate to severe patient neurologic presentation with a NIHSS score higher than 10 (p= .0001, p=.002, p = .002, respectively). On control CT, a large infarct core was significantly associated decreased serum level of sTRAIL and adropin (p= .001 and p= .000; respectively); however the levels of S100B were not significantly associated with good ASPECT score (p= .684). Disability and unfavorable outcome was significantly related with the decreased level of sTRAIL and adropin (p= .001 and p= .000; respectively for THRIVE score >5); whereas there was no significant relationship with serum S100B levels (p= .291 for THRIVE score >5). In the same manner, good prognosis at third month was significantly related to the level of sTRAIL and adropin (p= .001 and p= .000; respectively for mRS 0-2); whereas there was no significant relationship with the level of S100B (p= .291 for mRS 0-2). Decreased levels of sTRAIL with adropin and increased level of S100B were significantly corraleted with the presence of large artery atherosclerotic etiologic factor among study population (p= .000, p= .000, p = .036, respectively). Clinical and

laboratory parameters of the patients at admission to emergency department were demonstrated in Table 2. Previous researchers have shown that adropin is especially related to insulin resistance (16). In subgroup analysis, we found that six stroke patients with LAA have diabetes as a vascular risk factor and also twelve of them have decreased adropin levels. We did not find any relationship between the study biomarkers with vascular risk factors, admission serum glucose levels, and admission systolic-diastolic blood pressure levels. The study biomarkers (sTRAIL, Adropin, S100B) were compared with vascular risk factors using Mann-Whitney test. 39 study patients had more than one risk factor (43.3 %). The test revealed that only S100B level was significantly correlated with more than one risk factor (p= .013).

For subjects, the cut-off values of these biomarkers were calculated due to determine good clinical outcome and small infarct core. For S100B, the cut-off value was 427 ng/L; the sensitivity was 100%, the specificity was 100%, and the AUC was 1.000 based on the ROC curve. For sTRAIL, the cut-off value was 1705.93 ng/L; the sensitivity was 86%, the specificity was 66%, and the AUC was .143 based on the ROC curve. For adropin, the cut-off value was 388.7 pg/mL; the sensitivity was 98%, the specificity was 83%, and the AUC was .028 based on the ROC curve. ROC curve analyses of the biomarkers in predicting favorable outcome in stroke patients were demonstrated in figure 2.

Discussion

Ninety acute stroke patients have enrolled to our study and 24 of the patients had large artery atherosclerosis significant association with the predictor biomarkers of good clinical outcome and small infarct core.

Ongoing trials have proposed to determine a predictor biomarker to estimate post-stroke survival rate, disability, and final infarct core. S100B is a calcium-binding protein that has been a well-known serological biomarker of blood brain barrier dysfunction and damage after cerebral injury (17). Increased level of serum S100B protein could predict the severity of brain damage and survival rate. The recent study investigated that S100B protein was significantly correlated with final brain damage and early neurologic disability in 32 acute stroke patients (18). In a study conducted by Weglewski A et al, serum S100B protein concentrations of acute ischemic stroke patients, admitted to the hospital within 24 hours, showed significant correlation Between final infarct core for patients with moderate to severe stroke (11). Park et al. examined 111 acute stroke patients and they showed that serum S100B level was associated significantly with the early and late neurologic disability (19). We evaluated the study patients within 24 hours after stroke onset and our measurements in acute stroke patients showed the single-timing serum study biomarkers. Although the increased level of S100B protein has been evaluated more specifically for cerebral injury, the serum levels would be rise gradually within three-days after stroke onset. Possibly because of that, we found a significant association between the increased level of serum S100B protein and only initial NIH scores as an early neurologic outcome. Related to this finding, we could suggest that to determine any relationship between long-term neurological survival rate and the serum level of S100B protein, the blood sampling could be done 48-72 hours after stroke onset.

Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) has been analyzed in various disease pathophysiology TRAIL does not only induce apoptosis; indeed, the endothelial cell in the artery wall and inflammatory cells in atheroma plaque express TRAIL (20). Recently, the researches have shown that the level of serum TRAIL (sTRAIL) was correlated with stroke outcome seven days after stroke onset (21). Similarly, another study was evaluated that low sTRAIL level was associated with stroke severity in 293 patients seven days after stroke onset (22). Differently, we showed the biological significance of sTRAIL inversely related to both early and late neurological prognosis, final infarct core, and presence of large artery atherosclerosis within 24-hours stroke onset. TRAIL might be involved neuroprotective process in ischemic stroke.

Adropin plays a crucial role in vascular health and insulin sensitivity (16). Wu et al. discovered that decreased adropin levels in diabetic patients were significantly correlated with coronary atherosclerotic damage rather than non-diabetic ones in 392 patients with acute coronary syndrome (23). The researches have suggested that increased expression of adropin might positively affect the plaque stability and vascular elasticity to attenuate atherosclerosis on experimental study (24). Gu et al. discovered that adropin is negatively correlated with primary hypertension in 123 newly diagnosed patients (25). Similarly, the researchers reported that patients with cardiac syndrome X had lower adropin levels that other study patients (26). Altamimi et al investigated that adropin positively effect to cardiac metabolism associated with insulin resistance in an experimental study (27). In our study, we found low adropin levels were associated with large infarct core, initial and

long-term disability. And we showed that all stroke patients with diabetes had decreased adropin levels.

Atherosclerosis is an important mechanism of LAA stroke and the ongoing process involves the immune system response and vascular inflammation (14). Secchiro et al were investigated that plasma levels of TRAIL were lower for patients with myocardial infarction (28). Cartland et al concluded that TRAIL is protective of atherosclerosis by reducing inflammatory cells (29). Similarly, Sato et al suggested that adropin could contribute to antiatherosclerosis by modulating inflammatory molecule expression ans smooth cell proliferation (24). Indeed, in clinical studies, the researches found that the plasma level of adropin could contribute to the prevention of coronary artery diseases (30). With 3-month follow up, we found that plasma level of TRAIL and adropin negatively correlated with the prognosis of LAA as measured by mRS. In this study, we could suggest that TRAIL and adropin may be involved in the prognosis of LAA stroke. Plasma level of the biomarkers might be significant value in predicting the prognosis of patients with LAA stroke.

There were several limitations to our study. First, our study sample size was small; and the predictive cut-off values of serum adropin and TRAIL needs to be further confirmed in large-cohort studies. Secondly, studies that used other techniques, such as carotid ultrasonography that measured the intima-media thickness of the common carotid artery would be included to evaluate relationship with subclinical atherosclerosis and the serum biomarkers. Thus, we could determine high-risk patients without clinical manifestations. Thirdly, further studies could be more specifically evaluate the level of these

biomarker in atherosclerotic plaque or carotid tissue or saliva samples rather than serum levels. Because if saliva contains adropin and TRAIL; it would be advantageous, due to being non-invasive sampling, over testing the serum levels. And the last one, our measurements in acute stroke patients showed the single-timing serum adropin-TRAIL levels. Another study would be design to determine the temporal changes of the biomarker levels.

In summary, the influence of S100B, TRAIL and Adropin were determined on atherothrombotic cerebrovascular disease. The levels of S100B and TRAIL with Adropin were correlated inversely in acute stroke patients. Large infarct core, unfavorable early and late neurologic outcome were significantly associated with the study biomarkers. The study biomarkers as a sole biomarker are not sufficient to apply in the clinical risk assessment tools must be combined with a clinical risk score and neuroimaging data of stroke patients. Further investigations will be needed to apply especially TRAIL and Adropin soluble agent to acute stroke patients as a neuroprotective therapy.

Conflict of interest

The authors have no conflicts of interest to disclose.

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Table-1: Baseline characteristics of the patients at admission to emergency department. **Note.** Data in parentheses are percentages; † Data are the mean ± SD, data in parentheses are the range. (LAA-Large Artery Atherosclerosis; ASPECTS-Alberta Stroke Program Early Computed Tomography Score; NIHSS- The National Institutes of Health Stroke Scale; THRIVE-Totaled Health Risks in Vascular Events)

Characteristics	**All study patients (n=90)**	**LAA etiology (+) stroke patients (n=24)**	**LAA etiology (-) stroke patients (n=66)**
Demographics			
Age †	69.28 ± 10 (42 - 87)	63.88±10,75 (42-77)	71.24±9,02 (45-87)
Sex Female (n,%) Male (n,%)	 39 (43.3) 51 (56.7)	 12(13.3) 12(13.3)	 39(43.3) 27(30)
Medical and drug history			
Hypertension (n,%)	64 (71.1)	15(62,5)	49(74.2)
Diabetes Mellitus (n,%)	12 (13.3)	6(25)	6(50)
Hyperlipidemia (n,%)	27 (30)	8(33.3)	19(70.4)
Coronary Heart Disease (n,%)	20 (22.2)	7(29.2)	13(65)
Current Smoking (n,%)	15 (23.3)	1(4.2)	14(93.3)

Table-2: Clinical and laboratory parameters of the patients at admission to emergency department. **Note.** Data are the mean ± SD, data in parentheses are the range. (LAA-Large Artery Atherosclerosis; ASPECT-Alberta Stroke Program Early Computed Tomography Score; NIHSS- The National Institutes of Health Stroke Scale; THRIVE-Totaled Health Risks in Vascular Events)

Characteristics	**All study patients (n=90)**	**LAA etiology (+) stroke patients (n=24)**	**LAA etiology (-) stroke patients (n=66)**	**p value**
Clinical and laboratory parameters				
Glucose (mg/dl) at admission	138.07 ± 63.21 (76-350)	150.9±69.9 (89-350)	133.41±60.5 (76-350)	.657
Systolic blood pressure (mmHg) at admission	154.81 ± 33.43 (80-240)	159±26 (120-230)	153.3±35.8 (80-240)	.233
Diastolic blood pressure (mmHg) at admission	80 ± 13.58 (40-110)	82.92±12.61 (66-110)	78.95±13.84 (40-110)	.178
S100B (ng/L) at admission	976.33±543.75 (164.38-2906.44)	1174.93±611.61) (599.62-2678.58)	904.11±502.60 (164.38-2906.44)	**.036**
TRAIL (ng/L) at admission	2542.59±1382.9 (945.01-6580.75)	3501.82±1353.93 (1385.11-6580.75)	2193.76±1068.42 (945.01-5695.73)	**.000**
Adropin (pg/mL) at admission	240.62±91.60 (1131.11±455.23)	156.75±27.1 (113.11±198.42)	271.11±87.7 (122.62±455.23)	**.000**
ASPECT Score at admission	9.2 ± 1 (7-10)	8.42±1.21 (7-10)	9.48±0.75 (7-10)	**.000**
ASPECT Score at control (at 24th hr.)	7.4 ± 1.2 (4-9)	6.2±1.25 (4-9)	7.33±1 (5-9)	**.000**
NIHSS score at admission	17.08 ± 4.65 (4-25)	22.38±1.95 (19-25)	15.15±3.76 (4-20)	**.000**
THRIVE score at admission	4 ± 1.27 (1-7)	5.2±1.4 (2-5)	3.6±0.92 (1-7)	**.000**

Figure-1. Distribution of baseline and follow-up clinical scores to measure good clinical outcome and small infarct core in the study patients. (ASPECT-Alberta Stroke Program Early Computed Tomography Score; NIHSS- The National Institutes of Health Stroke Scale; THRIVE-Totaled Health Risks in Vascular Events; mRS-modified Rankin score)

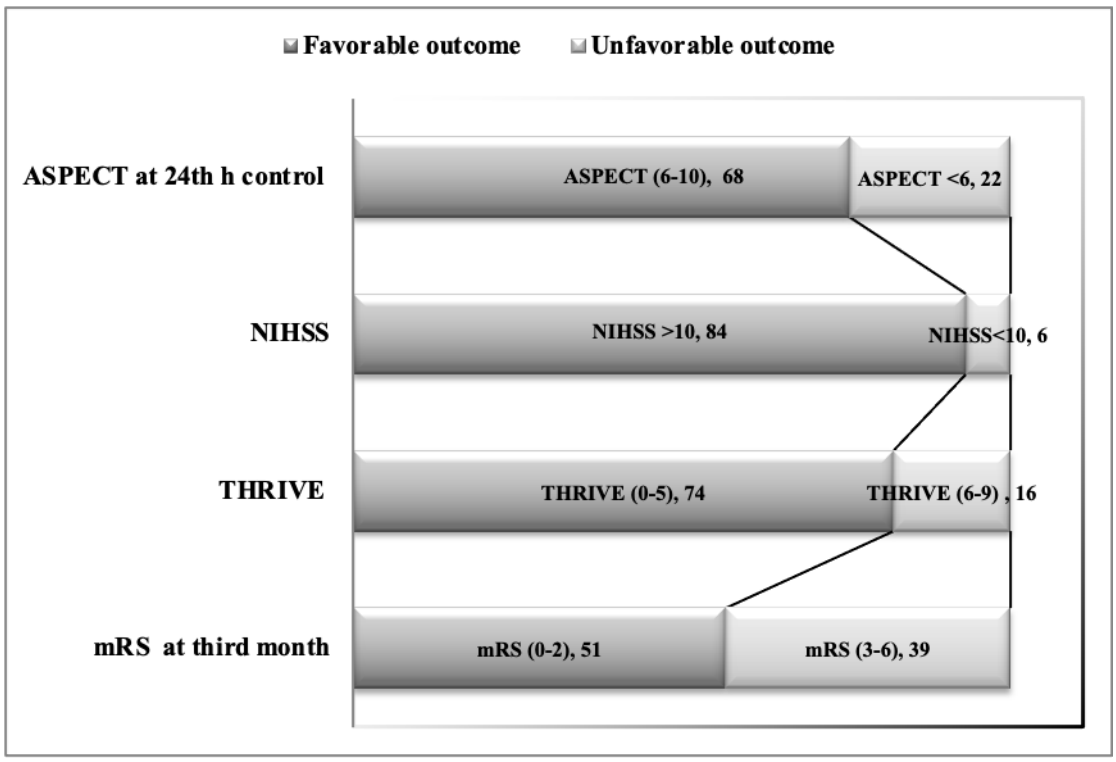

Figure-2: ROC curve analyses of the biomarkers in predicting favorable outcome in stroke patients (AUC = area under the curve; ROC = receiver operating characteristic; CI: Confidence Intervals)