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Original Article

Association between biomarkers in the long-term prognosis of ischemic stroke

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Abstract

Aim: Predicting of the stroke prognosis has utmost importance as the disease has a heavy socioeconomical burden. For this reason, instruments such as stroke severity scales, stroke volume calculations and various biomarkers are used for determination of prognosis. NIHS scale, stroke volume, stroke type, neutrophil/lymphocyte ratio and C-reactive protein levels were reported to be associated with stroke prognosis. In this study we aim to investigate the relationship between these parameters with 8-year-survival from stroke.

Materials and Methods: Between January 2010 and January 2012, all patients aged over 18 and diagnosed with arterial stroke were retrospectively investigated. Data regarding survival status were obtained from Death Reporting System (https://obs.gov.tr/) under the surveillance of Ministry of Health. NIHS scale, stroke volume, stroke subtype, neutrophil/lymphocyte ratio and C- reactive protein levels were obtained and compared in deceased and living patients and association between those parameters and survival was sought.

Results: Advanced age, male gender, NIHS scale, stroke volume, stroke subtype, neutrophil/lymphocyte ratio were associated with stroke survival. C-reactive protein levels were not be found associated.

Conclusion: Our results were consistent with the literature and, NIHS scale, stroke volume, stroke subtype, neutrophil/lymphocyte ratio predicted the stroke prognosis. As there is not enough data present in the literature, our findings were remarkable.

Keywords: Stroke severity; ischemia volume; neutrophil/lymphocyte ratio; C-reactive protein; prognosis.

INTRODUCTION

Stroke, which is defined by the World Health Organization as findings correlated with focal or global impairment of cerebral functions that rapidly develop and last for more than 24 hours or more or lead to death, affects approximately 33 million people worldwide every year and is more common in developing countries (1.2). Acute stroke is one of the common causes of morbidity and mortality across the globe (3). It is the third most common cause of death in our country (4). Since the mortality and morbidity rates are high, it is important to predict the early and late stage prognosis of these patients. Several studies were conducted in the literature to estimate the risk assessment and stroke prognosis (5-8).

The severity of stroke and the post-treatment functionality can be predicted by specific scales. In the studies conducted with (National Institute of Health Stroke Scale (NIHSS), which is one of these scales, it is reported that changes in the NIHSS scale and infarction volume are correlated with 90-day stroke outcomes in patients (5). However, a sufficient number of studies investigating the correlation between ischemic volume and prognosis are not available. Its effect on short and long-term prognosis is reported to be different (6). It is also reported that inflammatory markers such as C-reactive protein (CRP), TNF-alpha and interleukin-6 may be correlated with stroke prognosis (9.10). It is also reported that neutrophils play a key role in atherogenesis and atherothrombosis (11) and short-term mortality can be predicted based

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on neutrophil/lymphocyte (N/L) ratio (12). C-reactive protein is an indicator of systemic inflammation and several studies have demonstrated that it can predict atherosclerosis burden (13). Although a large number of studies indicate that CRP is correlated with an increased risk of stroke (14), some studies reporting that there is not any significant correlation are also available (15).

In the literature, a sufficient number of studies investigating the correlation between the long-term prognosis of ischemic stroke and these parameters are not available. Therefore, we aimed to investigate the correlation between NIHSS, ischemic volume, N/L ratio and CRP level and survival for approximately 8 years in patients with ischemic stroke.

MATERIALS and METHODS

The folders of patients older than 18 years, who were diagnosed with arterial ischemic stroke in the neurology clinic in January 2010 - January 2012, were retrospectively reviewed. Stroke classification was made with Trial of Org 10172 in Acute Stroke Treatment (TOAST). In this classification, it is divided into two groups as cardiac (cardiac embolism) and non-cardiac (large vessel occlusion, ischemic lacunar stroke, other determined etiology and unknown etiologies). The survival of patients were evaluated by their TR ID numbers in Republic of Turkey Ministry of Health, Directorate of Public Health, Death Notification System (https://obs.gov.tr/). If the patient died, the duration (in months) from ischemic stroke until death was noted whereas the duration from the ischemic stroke until the examination was noted for the surviving patient. NIHSS scores, neutrophil/lymphocyte ratios, cardiac arrhythmias, cardiac valve pathologies, systemic diseases other than wall pathologies (hypertension, diabetes mellitus, hyperlipidemia, chronic kidney, lung and liver diseases, thyroid disorders) were also noted from the folders of the patients. Those with a single systemic disease and those with at least two systemic diseases were studied separately. Ischemia volume was calculated by using the Analyze 11.0 program from the diffusion magnetic resonance imaging (MRI) taken at the time of diagnosis. Patients who had at least two different etiologies, had previously had stroke, developed hemorrhagic transformation, pregnant women, postpartum patients, patients with intracranial space-occupying lesion and demyelinating disease, those with malignancy or rheumatologic disease and those who died during their follow-up were not included in the study. In addition, cases with missing data in any of the parameters were not included in the study (Figure 1).

All MRI examinations were made with a 1.5 T MRI scanner (Magnetom Avanto, Siemens Healthcare, Forcheim, Germany). All patients included in the study had diffusion-weighted imaging. The volume of ischemia was measured by a single radiologist who was blind to patient data. Evaluation was calculated with Analysis 11.0 software (Analyze Direct Inc., Kansas City, USA).

This study was approved by our corporate ethics committee and written informed consent for all matters was obtained.

Statistical Analysis

The consistency of data with normal distribution was compared with the D'Agostino-Pearson test. Nominal variables were compared by chi-square test. Data related to survival were analyzed by logistic regression model and independent factors were evaluated. Two independent sampling T-tests were used for parameters with normal distribution. The value of <0.05 was accepted as significant for two-way p-value. All statistical analyzes were conducted with Medcalc program (Medcalc ver 12, Ostend, Belgium).

RESULTS

A total of 136 patients (65 with cardiac ischemic stroke and 71 with non-cardiac ischemic stroke) with a follow-up of 8 years were evaluated. From the patients with non-cardiac ischemic stroke, 36 had large vessel occlusion, 27 had ischemic lacunar stroke, 7 had other determined etiology (dissection (1), vasculitis (1), antiphospholipid antibody syndrome (1), and other hypercoagulable states (4)) and 1 had unknown etiology. The mean age of the dead and surviving cases were 73.3 and 62.5, respectively, and a statistically significant difference was found (Table-1). 44.9% (n=61) of the patients were male. Death rates within the first year were 16.9% for the cardiac stroke and 26.8% for the non-cardiac stroke. A significant difference was found between the stroke sub-types and the groups, and the mortality rate was higher in the non-cardiac stroke group (p=0.026). Demographic and study data belong to survived and died patient groups were given in Table 1 with corresponding p values. Age, gender, type of stroke,

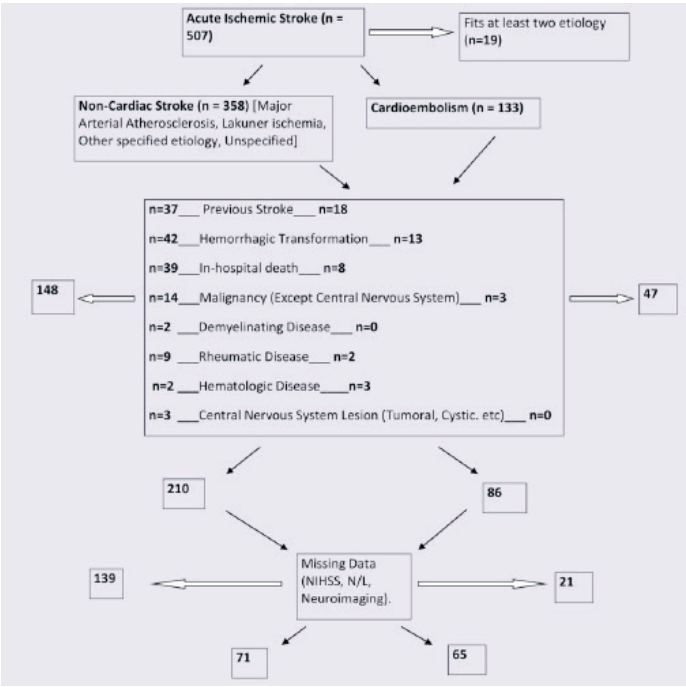

Figure 1. Inclusion and exclusion criteria

NIHSS scores, volume of ischemia, N/L rates, CRP levels and their effects on survival were assessed with logistic regression analysis. All parameters except for CRP levels were independently associated with 8-year survival (Table-2).

DISCUSSION

In our study, long-term prognosis of cardiac and non-cardiac ischemic stroke was investigated and interesting findings were obtained. Ischemic stroke is one of the major causes of death in many countries. Mortality in the first year of the disease ranged between 21% and 30%, while permanent disability was reported in 15-30% of the survivors (16.17). When the socio-economic burden of patients with ischemic stroke is evaluated, knowing the prognosis of patients is important for planning additional measures, treatment and care. Thus, different markers were used to predict the prognosis (volume of ischemia, stroke severity scales, serum biomarkers etc.) (5.8.10.12.18). The severity of first stroke is an important indicator of the clinical outcome for patients with acute ischemic stroke. Different scales are used for determining the severity of stroke (19.20). NIHSS scale is one of the most commonly used scales. In a study where NIHSS scale was used, it was found to be correlated with the prognosis (19). Similarly, in a study investigating hospital mortality rates, it was found that advanced age and high NIHSS scores were correlated with the mortality rate (7). In a study where short and long-term prognosis in elderly patients with stroke was investigated, NIHSS scores were found to be correlated with both factors (21). A sufficient number of studies investigating the correlation between long-term prognosis and gender are not available in the literature. In a study investigating ninety-day survival, a significant correlation between age and survival was reported, but no correlation was found between 90-day survival and gender (20). In a study where 5-year-survival in patients with ischemic lacunar stroke was investigated, a correlation was found between age and male gender and death (22). Male gender is reported to be correlated with long-term negative outcome in ischemic strokes in young adults (23). Although any difference between 1-year survival and gender was not found in another study, mortality was demonstrated to be higher in older women (> 85). We also ascertained that 22.1% of the patients died in the first year, which is consistent with the literature. Our findings indicate that NIHSS scores of patients are a good predictor of long-term prognosis. In our study, a significant difference was found between the mean NIHSS scores of the groups of surviving and dead patients. The mean age of the the group of dead patients was significantly higher than the mean age of the surviving group. According to the logistic regression analysis, age and high NIHSS scores had a negative effect on survival. No difference was found between the groups of surviving and dead patients by means of gender, which

Table-1: Stroke variables in groups of surviving and dead patients and the corresponding p-values.

	Dead (n=69)	Surviving (n=67)	Total	p
Mean age ± ss	73.3±10.1	62.5±11.4	69.3 ± 11.5	**<0.001**
Gender				
Male, number (%)	33 (47.8)	28 (41.8)	61 (44.9)	0.592
Type of Stroke, number (%)				
Cardiac	26 (37.7)	39 (58.2)	65 (47.8)	**0.026**
Non-Cardiac	43 (62.3)	28 (41.8)	71 (52.2)	
Cigarettes, number (%)	23 (33.3)	20 (29.9)	43 (31.6)	0.809
Alcohol, number (%)	4 (5.8)	4 (6)	8 (5.9)	0.913
At least one systemic disorder, number (%)	39 (56.5)	28 (41.8)	67 (49.3)	0.122
At least two systemic disorders, number (%)	21 (30.4)	9 (13.4)	30 (22.1)	**0.029**
Mean NIHSS	10	5	7	**<0.001**
Mean stroke volume, cm3	27.09	16.49	5.58	**0.001**
Mean N/L ratio	2.3	1.6	1.97	**<0.001**
Mean CRP	2.5	0.8	1.7	**<0.001**

Table 2. Logistic regression analysis of survival for approx. 8 years and other parameters

	Fixed	Standard Error	p
Age	-0.124	0.048	**0.009**
Gender (Male)	-2.31	0.979	**0.018**
NIHSS	-0.29	0.117	**0.012**
Volume	-0.00007	-0.000003	**0.013**
Type of Stroke (Cardiac)	1.99	0.921	**0.031**
N/L	-2.34	0.751	**0.018**
CRP	-0.333	0.239	0.163

was consistent with the literature. However, male gender was found to have a negative effect on 8-year survival.

In the literature, it was reported that early neurological impairment and initial NIHSS scores and ischemia volume were correlated. In a study investigating the 6-month prognosis, the ischemia volume was reported to be correlated with prognosis (26). In a study conducted on patients with moderate cerebral artery occlusion who were administered endovascular treatment, the ischemia volume was found to be correlated with clinical improvement (27). In the aforementioned studies, the correlation between long-term prognosis and ischemia volume has not been studied and a sufficient number of studies on long-term prognosis are not available in the literature. In a study investigating the ischemia volume with short and long-term prognosis, it was reported that ischemia volume may be a marker for short-term prognosis but the same conclusion is not valid for long-term (6). In our study, we found that the ischemia volume was different between the dead and the surviving groups, and the mean ischemia volume was higher in the group of dead patients. We also determined by logistic regression analysis that the ischemia volume has a negative effect on survival.

A sufficient number of studies investigating the correlation between sub-types of ischemic stroke and prognosis are not available in the literature. In a study where a two-year prognosis was investigated in sub-types of ischemic stroke, mortality was reported to be correlated with large vessel occlusion and stroke sub-type was effective in predicting the long-term prognosis (28). In a study investigating a 5-year prognosis in patients with ischemic lacunar stroke, it was reported that poor prognosis rate was higher compared to the normal population after the first several years (22). In our study, a statistically significant difference was found between the rates of deceased patients in cardiac and non-cardiac stroke groups. The mortality rate was higher in the non-cardiac group and cardiac stroke had a positive effect on survival for approximately 8 years. In our non-cardiac group, the majority of patients had large vessel occlusion which was followed by ischemic lacunar stroke.

It has been reported in the literature that ischemia prognosis and survival were determined by multiple factors (29). In a large-scale study, the incidence of another medical condition in patients with stroke was reported to be higher compared to the non-stroke group. In the same study, the number of other medical conditions was found to be correlated with the stroke (30). In a large-scale study with 9-year follow-up, multiple comorbid condition was reported to be an independent predictor of poor prognosis (31). Our findings were consistent with the literature and a significant statistical difference was found between the groups regarding the presence of at least two or more systemic diseases.

Recent clinical studies have shown that high N/L levels have predictive power for the prognosis, severity and mortality rates of atherosclerosis, cardiovascular and cerebrovascular diseases (32.33).

In some studies, neutrophils have been demonstrated to cause neutrophil invasion and plaque rupture by secreting mediators such as proteolytic enzymes, arachidonic acid, elastase and free oxygen radicals (34.35). In particular, it has been reported that the initial neutrophil count increases the severity of ischemic injury and causes poor neurological prognosis (12). Acute ischemic stroke was reported to be correlated with high N/L ratio (36). In another study, it was reported that N/L ratio and C-reactive protein elevation in the first 24 hours of acute ischemic stroke were correlated with poor prognosis (37). CRP is an indicator of inflammation in both acute and chronic systemic inflammation (38). In an autopsy study, CRP density in atherosclerotic coronary arteries was reported to be correlated with intimal thickness (39). In addition, studies have demonstrated that high CRP level is a strong risk factor for fatal stroke (40). In our study, we found a significant difference between the N/L ratio and CRP levels between the groups of dead and surviving patients, both of which were higher in the group of dead patients. Among the parameters of N/L ratio and CRP levels, only N/L ratio was associated with long-term survival.

The requirement for predicting the prognosis of the disease is important as caretakers should plan the measures such as treatment and rehabilitation of stroke patients since the number of elderly people is increasing and patients with ischemic stroke is more frequently encountered. Therefore, we think that the results of our study are remarkable, but further studies on a larger sampling group will provide us more objective results.

Our study reflects long-term results for predicting the prognosis in patients with ischemic stroke. Age, gender, NIHSS, ischemia volume and N/L ratios may serve as a guide for the prediction of long-term prognosis. The burden of systemic disease also affects the survival of patients.

Competing interests: The authors declare that they have no competing interest.

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REFERENCES

1. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke 2013;44:2064-89.
2. Bender M, Jusufovic E, Railic V, et al. High Burden of Stroke Risk Factors In Developing Country: The Case Study Of Bosnia-Herzegovina. Mater Sociomed 2017;29:277-9.
3. Lopez AD, Mathers CD, Ezzati M, et al. Global and regional

burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 2006;367:1747-57.
4. Onat A, Hergenc G, Can G. Prospective validation in identical Turkish cohort of two metabolic syndrome definitions for predicting cardiometabolic risk and selection of most appropriate definition. Anatol J Kardiol 2007;7:29-34.
5. Sajobi TT, Menon BK, Wang M, et al. Early Trajectory of Stroke Severity Predicts Long-Term Functional Outcomes in Ischemic Stroke Subjects: Results From the ESCAPE Trial (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times). Stroke 2017;48:105-10.
6. Wang J, Yu XD, Li GQ. Comparative study on short-term and long-term prognostic determinants in patients with acute cerebral infarction. Int J Clin Exp Med 2015;8:9855-61.
7. Su YC, Huang KF, Yang FY, et al. Elevation of troponin I in acute ischemic stroke. Peer J. 2016; 4:1866.
8. Ceylan M, Yalcin A, Bayraktutan OF, et al. Serum pentraxin-3 levels in acute stroke: No association with stroke prognosis. Atherosclerosis 2015;243:616-20.
9. Domac FM, Somay G, Misirli H, et al. Tumor necrosis factor alpha serum levels and inflammatory response in acute ischemic stroke. Neurosciences (Riyadh) 2007;12:25-30.
10. VanGilder RL, Davidov DM, Stinehart KR, et al. C-reactive protein and long-term ischemic stroke prognosis. J Clin Neurosci 2014;21:547-53.
11. Horne BD, Anderson JL, John JM, et al. Which white blood cell subtypes predict increased cardiovascular risk? J Am Coll Cardiol 2005;45:1638-43.
12. Tokgoz S, Keskin S, Kayrak M, et al. Is neutrophil/lymphocyte ratio predict to short-term mortality in acute cerebral infarct independently from infarct volume? J Stroke Cerebrovasc Dis 2014;23:2163-8.
13. Khera A, de Lemos JA, Peshock RM, et al. Relationship between C-reactive protein and subclinical atherosclerosis: the Dallas Heart Study. Circulation 2006;113:38-43.
14. Di Napoli M, Papa F, Bocola V. C-Reactive Protein in Ischemic Stroke: An Independent Prognostic Factor. Stroke 2001;32:917-24.
15. Wilson PW, Nam BH, Pencina M, et al. C-reactive protein and risk of cardiovascular disease in men and women from the Framingham Heart Study. Arch Intern Med 2005;165:2473-8.
16. D. Lloyd-Jones, R. Adams, M. Carnethon, et al. Heart disease and stroke statisticse 2009 update: a report from the American heart association statistics committee and stroke statistics subcommittee. Circulation 2009;119:480-6.
17. Utku U, Çelik Y. Strokta Etyoloji, Sınıflandırma ve Risk Faktörleri. Serebrovasküler Hastalıklar ed. Balkan S, editor. Antalya: Güneş Kitapevi; 2005;57-71.
18. T. Brott, J.R. Marler, C.P. Olinger, et al. Measurements of acute cerebral infarction: lesion size by computed tomography. Stroke 1989; 20:871-5.
19. Mar J, Masjuan J, Oliva-Moreno J, et al. Outcomes measured by mortality rates, quality of life and degree of autonomy in the first year in stroke units in Spain, HealthQual. Life Outcomes 2015; 13:36.
20. Wei W, Li S, San F, et al. Retrospective analysis of prognosis and risk factors of patients with stroke by TOAST. Medicine (Baltimore) 2018;97:0412.
21. Hsu CY, Hu GC, Chen YM, et al. Predictors of short- and long-term mortality in first-ever ischaemic older stroke patients. Australas J Ageing 2013;32:229-32
22. Staaf G, Lindgren A, Norrving B. Pure motor stroke from presumed lacunar infarct: long-term prognosis for survival and risk of recurrent stroke. Stroke 2001;32:2592-6.
23. Varona JF, Bermejo F, Guerra JM, et al. Long-term prognosis of ischemic stroke in young adults. Study of 272 cases. J Neurol 2004;251:1507-14.
24. Bang OY, Park HY, Yoon JH, et al. Predicting the Long-Term Outcome after Subacute Stroke within the Middle Cerebral Artery Territory. J Clin Neurol 2005;1:148-58.
25. Zaidi SF, Aghaebrahim A, Urra X, et al. Final infarct volume is a stronger predictor of outcome than recanalization in patients with proximal middle cerebral artery occlusion treated with endovascular therapy. Stroke 2012;43:3238-44.
26. Redfors P, Jood K, Holmegaard L, Rosengren A, Blomstrand C, Jern C. Stroke subtype predicts outcome in young and middle-aged stroke sufferers. Acta Neurol Scand2012;126:329-35.
27. K.B. Slot, E. Berge, P. Dorman, et al. Impact of functional status at six months on long term survival in patients with ischaemic stroke: prospective cohort studies, BMJ 2008;336:376-9
28. Chu LM, Liu CC, Yeh CC, et al. Increased diabetes risk and interaction with social and medical events in patients upon stroke: Two nationwide studies. Atherosclerosis 2017;265:87-92.
29. Castro HHG, Alencar AP, Benseñor IM, et al. Multimorbidities Are Associated to Lower Survival in Ischaemic Stroke: Results from a Brazilian Stroke Cohort (EMMA Study). Cerebrovasc Dis 2017;44:232-9.
30. Papa A, Emdin M, Passino C, et al. Predictive value of elevated neutrophil-lymphocyte ratio on cardiac mortality in patients with stable coronary artery disease. Clin Chim Acta 2008;395:27-31.
31. Gibson PH, Croal BL, Cuthbertson BH, et al. Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting. Am Heart J 2007;154:995-1002.
32. Azab B, Zaher M, Weiserbs KF, et al. Usefulness of neutrophil to lymphocyte ratio in predicting short- and long-term mortality after non-ST-elevation myocardial infarction. Am J Cardiol 2010;106:470-6.
33. Muhmmed Suliman MA, Bahnacy Juma AA, Ali Almadhani AA, et al. Predictive value of neutrophil to lymphocyte ratio in outcomes of patients with acute coronary syndrome. Arch Med Res 2010;41:618-22.
34. Balestrino M, Partinico D, Finocchi C, Gandolfo C. White blood cell count and erythrocyte sedimentation rate correlate with outcome in patients with acute ischemic stroke. J Stroke Cerebrovasc Dis 1998;7:139-44.
35. Christensen H, Boysen G. C-reactive protein and white blood cell count increases in the first 24 hours after acute stroke. Cerebrovasc Dis 2004;18:214-9.
36. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 1999;340:448-54.
37. Zhang YX, Cliff WJ, Schoefl GI, et al. Coronary C-reactive protein distribution: its relation to development of atherosclerosis. Atherosclerosis 1999;145:375-9.
38. Gussekloo J, Schaap MCL, Frolich M, et al. C-Reactive Protein Is a Strong but Nonspecific Risk Factor of Fatal Stroke in Elderly Persons. Arterioscler Thromb Vasc Biol 2000;20:1047-51.

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