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Diagnostic Value of the Fibrinogen-to-Albumin Ratio in Acute Ischemic Stroke

Fibrinojen Albümin Oranının Akut İskemik İnmede Tanısal Önemi

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Abstract

Objective: Previous research suggests that high levels of fibrinogen and low levels of albumin are associated with the occurrence of ischemic stroke and the severity of the disease. As a recently described rational parameter, the fibrinogen-to-albumin ratio (FAR) has been studied in several conditions associated with inflammation and pro-coagulation, such as retinal venous occlusion, coronary artery disease, and cancers. This study aims to research the usefulness of FAR when diagnosing ischemic stroke and the prediction of its severity and prognosis.

Materials and Methods: The study involved 52 patients with acute ischemic stroke and 39 control cases between the ages of 18 and 80. The demographics, medical history, primary diagnosis, examination findings, imaging findings, and laboratory tests of all patients were derived from our hospital records. Stroke severity was classified into three groups: mild, moderate, and severe. The FAR values were compared between the stroke and control groups and between the stroke severity groups. For statistical analysis, SPSS 23.0 (IBM) was used, and $P < 0.05$ was considered significant.

Results: Fibrinogen levels and FAR values were significantly higher and albumin levels lower in the patients with stroke than in the control group ($P < 0.001$). The FAR cut-off value was 6.65 for the diagnosis of acute ischemic stroke; it was more sensitive and specific than albumin and fibrinogen. There were no significant differences between the severity stages of stroke, the etiologic subgroup of stroke, length of hospitalization, and short-term prognostic effect on patients with stroke in terms of FAR, fibrinogen, and albumin ($P > 0.05$).

Conclusion: This study suggests that FAR would be an innovative, sensitive, and specific diagnostic marker for patients with acute ischemic stroke. However, it would be insufficient to predict stroke severity, etiology, and short-term prognosis.

Keywords: Fibrinogen-to-albumin ratio, fibrinogen, albumin ratio, ischemic stroke, prognosis

Öz

Amaç: Geçmiş çalışmalarda yüksek fibrinojen ve düşük albümin düzeyleri, iskemik inme oluşumu ve hastalık şiddeti ile ilişkilendirilmiştir. Fibrinojen-albümin oranı (FAO); enflamasyon göstergesinde yakın dönemde tanımlanan bir oransal parametredir. FAO, retinal ven tıkanıklığı, koroner arter hastalığı, kanserler gibi enflamasyon ve prokoagülasyon ile ilişkili birçok hastalık üzerinde çalışılmıştır. Biz bu çalışmada; FAO'nun iskemik inmenin tanısındaki, şiddetini ve prognoz öngörmedeki olası değerini araştırmayı amaçladık.

Gereç ve Yöntem: Yaşları 18 ile 80 arasında olan 52 akut iskemik inme hastası ve 39 kontrol olgusu çalışmaya dahil edildi. Tüm hastaların demografik özellikleri, tıbbi öyküleri, ön tanıları, muayene bulguları, görüntüleme özellikleri ve laboratuvar testleri hasta dosyalarından elde edildi. İnme şiddeti hafif, orta ve ağır olarak gruplandırıldı. FAO değerleri, inme-kontrol olguları arasında ve inme şiddeti grupları arasında kıyaslandı. İstatistiksel analizler için SPSS 23,0 (IBM) programı kullanıldı, $P < 0,05$ anlamlı olarak kabul edildi.

Bulgular: İnme grubunda ortalama FAO değeri, fibrinojen düzeyleri kontrol grubuna kıyasla daha yüksek, albümin düzeyi daha düşük idi ($P < 0,001$). Çalışmamızda FAO'nun en ideal eşik değeri 6,65 olarak saptanmış olup, albümin ve fibrinojene kıyasla duyarlılık ve özgüllüğü daha yüksekti. İnme şiddeti grupları, inme etiyolojik alt grupları, yatış süresi, kısa dönem prognostik fonksiyonel sonuç arasında ortalama FAO değerleri, albümin ve fibrinojen düzeyleri açısından anlamlı bir farklılık bulunmadı ($P > 0,05$).

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Sonuç: Çalışmamıza ait bulguları, FAO'nun inme olgularında yeni, duyarlılığı ve özgüllüğü yüksek bir diagnostik belirteç olabileceğini gösterse de, inmenin şiddeti, etiyolojisi ve prognozunu öngörmede yetersiz kaldığını düşündürmektedir.
Anahtar Kelimeler: Fibrinojen-albümin oranı, fibrinojen, albümin, iskemik inme, prognoz

Introduction

Ischemic stroke is a common health problem with a severe socioeconomic impact in addition to its mortality and morbidity. Approximately 80% of all stroke cases are acute ischemic stroke (1). The immune response and inflammatory process in acute cerebral ischemia are significant factors in the initiation and progression of stroke and functional loss (2). Many cell groups, such as blood cells, platelets, and endothelial cells, actively contribute to the inflammatory process (3). It is known that inflammatory parameters such as C-reactive protein (CRP), white blood cell count, and serum amyloid A increase in the early stages of ischemic stroke (4). Studies have associated the elevation of inflammatory parameters with the size of the ischemic lesion, functional outcomes of stroke, and clinical severity (5). Positive and negative acute phase reactants might individually provide valuable information about the severity of inflammation. However, a combination of these values could be more effective.

Fibrinogen is the most abundant clotting factor and a positive acute phase reactant protein of inflammation (6). Plasma fibrinogen levels have been found to increase in acute and chronic ischemic stroke (7). Albumin is a negative acute phase protein of inflammation and has inhibitor effects on platelet aggregation and thrombus formation (8). Several studies have discovered lower levels of albumin in venous thromboembolism and other ischemic events (9,10).

The fibrinogen-to-albumin ratio (FAR) has been found to be more sensitive and specific as a predictor of the progression of hypercoagulation and inflammation than fibrinogen (11). Moreover, FAR has a higher specificity and sensitivity than fibrinogen in predicting the severity of chronic venous insufficiency, a progressive inflammatory disease (10). Currently, there are no precise data regarding the predictive role of FAR in the vascular risk classification and prognosis of ischemic stroke. This study aims to demonstrate the changes in FAR values of patients with acute ischemic stroke and the prognostic value of FAR and analyze the efficacy of FAR compared with fibrinogen and albumin in patients with ischemic stroke.

The exclusion criteria were as follows: (i) history of previous stroke; (ii) acute infection within 2 weeks of admission or chronic infection; (iii) cancer, severe hepatic disease (alanine transaminase or aspartate transaminase >5 times the upper limit of normal), and renal diseases (estimated glomerular filtration rate <30 ml/min or end-stage renal disease requiring dialysis); (iv) hematological disease; (v) coronary artery disease; (vi) use of drugs that may cause hematological side effects (such as antiaggregants, oral contraceptives, steroids) before admission; (vii) intravenous thrombolysis or endovascular treatment; and (viii) treatment with defibrase or human albumin therapy.

Materials and Methods

Adult patients with acute ischemic stroke between 18 and 80 years of age who were admitted to Sakarya University Faculty of Medicine Training and Research Hospital between April 2020 and June 2021 were included in the study. The clinical, radiology, and laboratory data of the patients were analyzed retrospectively. Patients without data on albumin or fibrinogen during the initial 24 hours of ischemic stroke were excluded. The control group consisted of hospital staff health screening records.

Ischemic stroke was defined by (i) the presence of new-onset neurologic symptoms that were confirmed by neurologists, (ii) the exclusion of the presence of hemorrhage noted on a brain computed tomography scan, and (iii) a corresponding acute cerebral infarction with diffusion magnetic resonance imaging. The FAR was calculated from concurrent fibrinogen and albumin measurements and recorded within the first 24 hours of ischemic stroke onset.

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The demographics, medical history, primary diagnosis, examination findings, laboratory tests, and imaging findings of the patients were obtained from medical records. Hypertension, diabetes mellitus, coronary heart disease, and chronic obstructive pulmonary disease were accepted as chronic systemic diseases. National Institutes of Health Stroke Scale (NIHSS) scores were noted on admission and discharge. The NIHSS score consists of the sum of 15 separately evaluated components and scores range from 0 to 42 (12). Patients were categorized according to stroke severity into three groups: an NIHSS score ≤8 was defined as mild, an NIHSS score from 9 to 15 as moderate, and an NIHSS score ≥16 as severe stroke. The etiological classification was based on the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria (13). It denotes five sub-types of ischemic stroke: large-artery atherosclerosis, cardioembolism, small-vessel occlusion (lacunary infarction), stroke of other determined etiology, and stroke of undetermined etiology. Serum albumin and fibrinogen levels and serum coagulation parameters were concurrently tested within the first 24 hours of admission.

A poor functional outcome was defined as a modified Rankin scale (mRS) score of 3 to 6 (disability/death), and a good functional outcome was defined as an mRS score of 0 to 2 (independence) (14,15).

Statistical Analysis

Statistical analysis was performed using the SPSS 23.0 (IBM) statistical software program. The Kolmogorov–Smirnov test or Shapiro–Wilk test was used to determine whether the data distribution was normal. Descriptive statistics were expressed

as mean ± standard deviation if data were distributed normally, median and minimum–maximum if not. Categorical variables were defined as the number of cases and percentage (%).

Levene's test evaluated the homogeneity of numerical data with normal distribution. Homogeneous numerical data were compared using Student's t-test. Numerical data without normal distribution and/or homogeneity were compared with the Kruskal–Wallis and Mann–Whitney U tests for subgroup analysis. For the correlation analysis, the Pearson test was used. All reported statistical tests were two-sided, and $P < 0.05$ was considered significant.

Ethical committee approval (decision date: August 01, 2021, number: 47674) for this study was obtained from the Sakarya University Faculty of Medicine Ethical Committee.

Results

The study included 52 patients with acute ischemic stroke and 39 control cases. There were 27 male (48.1%) and 25 female (51.9%) patients with stroke and 13 male (33.3%) and 26 female (66.7%) control cases. The median age of the patients was 74 (51–80) years in the stroke group and 72 (53–80) years in the control group. Therefore, the median ages of the stroke and control groups were similar ($P = 0.292$). In our study population, 38 (73.1%) patients had at least one chronic disease; the most common was hypertension. The rates of atrial fibrillation and smoking were similar in both sexes (Table 1).

The median NIHSS score of patients was 7 (1–22), and the median NIHSS score of the male patients was significantly lower than that of the female patients (5 vs. 10; $P = 0.018$) (Table 2). The NIHSS scores were similar between smokers and non-smokers and patients with and without hypertension or diabetes mellitus. The average hospitalization duration was 8.5 days (2–32) (Table 2). The median hospitalization duration was significantly longer in female patients than in male patients ($P = 0.042$).

The median FAR value was 10.57 (5.29–124.33) and was similar for both male and female patients in the stroke group. The FAR values and fibrinogen levels were significantly increased, and albumin levels were decreased in the acute ischemic stroke group compared with the control group ($P < 0.01$ in all tests) (Table 3). The cut-off FAR value was 6.65 for the diagnosis of acute ischemic stroke, and it was more sensitive and specific than albumin and fibrinogen (Graphic 1, Table 4). When the patients were grouped according to the severity of the disease, there was no significant difference in FAR values, fibrinogen levels, or albumin levels ($P = 0.825$, $P = 0.959$, $P = 0.679$, respectively) (Table 5), reflecting the severity of acute ischemic stroke. Thus, there was no significant correlation between ischemic stroke severity according to NIHSS score, FAR value, or fibrinogen and albumin levels ($P = 0.615$, $P = 0.789$, $P = 0.417$, respectively).

According to the TOAST classification, the mean of the FAR values and fibrinogen and albumin levels were not significantly

Table 1. Ages and chronic disease distribution by sex

	Male (n = 27)	Female (n = 25)	Total (n = 52)	*P*
Age	71 (51–80)	75 (51–80)	74 (51–80)	0.073*
Hypertension	17 (63%)	17 (68%)	34 (65.4%)	0.776**
Diabetes mellitus	5 (18.5%)	9 (36.0%)	14 (26.9%)	0.215**
Atrial fibrillation	8 (25.8%)	4 (15.38%)	12 (23.1%)	0.142**
COPD	0	0	0	n/a
Smoking	12 (38.7%)	7 (26.9%)	19 (36.5%)	0.219**
Alcohol consumption	0	0	0	n/a

*Mann–Whitney U test, **chi-square, COPD: Chronic obstructive pulmonary disease, n/a: Not applicable

Table 2. Mean hospitalization duration, NIHSS distribution by sex

Parameters	Male (n = 27) Median (min–max)	Female (n = 25) Median (min–max)	Total (n = 52) Median (min–max)	*P* value*
NIHSS	5.0 (1–17)	10 (2–22)	7.0 (1–22)	0.018*
Hospitalization duration	6 (2–32)	10 (3–32)	8.5 (2–32)	0.042*

*Mann–Whitney U test, NIHSS: National Institutes of Health Stroke Scale, min: Minimum, max: Maximum

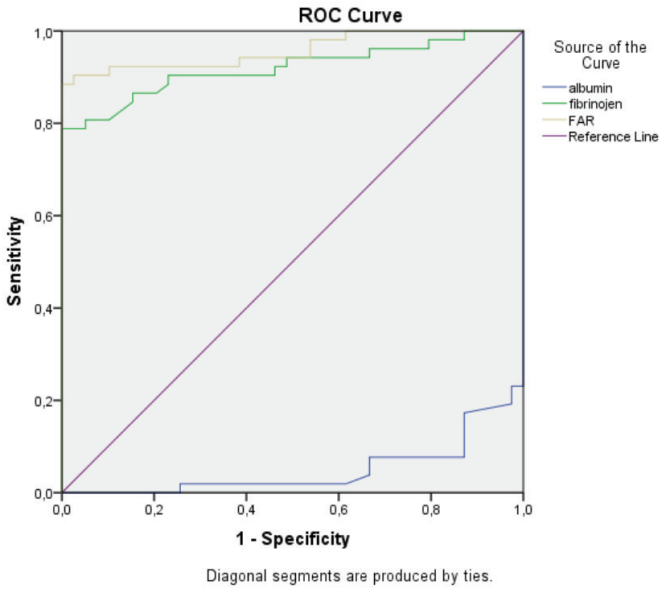
Table 3. Distribution of patients' fibrinogen, albumin, and FAR in the stroke and control groups

	Acute ischemic stroke (n = 52)	Control (n = 39)	*P*
Age	74 (51–80)	72 (53–80)	0.293*
FAR	10.57 (5.29–124.33)	5.54 (3.93–6.82)	<0.001*
Fibrinogen	352.50 (201.70–853)	240 (161–290)	<0.001*
Albumin	33.76 (3–45.36)	44 (38–48)	<0.001*

*Mann–Whitney U test, FAR: Fibrinogen-to-albumin ratio

different between sub-groups (P = 0.205, P = 0.250, P = 0.179, respectively) (Table 6).

The median of the FAR values and fibrinogen and albumin levels were not significantly different between the patients with a hospitalization period longer than 1 week and those with less than 1 week of hospitalization (P = 0.54, P = 0.89, P = 0.14, respectively) (Table 7). There was no significant association between poor and good functional outcomes according to the mRS score in terms of FAR values or fibrinogen and albumin levels (P = 0.341, P = 0.789, P = 0.197, respectively).



Graphic 1. ROC curve analysis of FAR, fibrinogen, and albumin

ROC: Receiver operating characteristic, FAR: Fibrinogen-to-albumin ratio

Discussion

In this study, we found that FAR values and fibrinogen levels were significantly increased and albumin levels were decreased in patients with acute ischemic stroke. The FAR cut-off value was more sensitive and specific than albumin and fibrinogen in determining acute ischemic stroke. Moreover, there was no significant correlation between disease severity according to NIHSS and FAR values, albumin levels, or fibrinogen levels in ischemic stroke. Many studies have identified increased fibrinogen in patients with acute ischemic stroke, but its association with disease severity is inconsistent. Studies have demonstrated that disease severity could be associated with high fibrinogen levels (16,17). Additionally, some studies suggest that a higher fibrinogen level is related to the presence of ischemic stroke but not disease severity on admission (18,19). This discrepancy could result from differences in hospital admission times or the application of different severity scales. Moreover, in previous studies, lower albumin levels have been associated with ischemic stroke and its severity according to NIHSS on admission (20,21). There are limited studies regarding the relationship between ischemic stroke and FAR, with different conclusions in the current literature, necessitating confirmation with further studies (22,23). In addition, to the best of our knowledge, no studies are currently researching the possible associations between FAR levels

Table 4. Determination of the cut-off value for the FAR, fibrinogen, and albumin according to a ROC curve analysis

Parameter	Cut-off value	Sensitivity	Specificity	Likelihood ratio	AUC	95% CI	*P* value
FAR	6.6553	90	97	35.25	0.958	0.91–0.99	<0.001
Fibrinogen	287.5000	80	94	15.75	0.919	0.86–0.97	<0.001
Albumin	42.0500	77	92	0.11	0.049	0.008–0.09	<0.001

FAR: Fibrinogen-to-albumin ratio, ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval

Table 5. Distribution of FAR, fibrinogen, and albumin values according to the disease severity of the patients

Parameters	Mild (NIHSS 0–8) median (min–max)	Moderate (NIHSS 9–15) median (min–max)	Severe (NIHSS >16) median (min–max)	*P* value*
FAR	10.74 (5.29–124.33)	11.66 (6.95–101.20)	10.44 (6.45–106.58)	0.823*
Fibrinogen	347.50 (201.70–853)	337 (294–493)	373 (229–431)	0.959*
Albumin	33.90 (3–45.36)	32.60 (3–42.30)	34.8 (4–39.58)	0.679*

*Kruskal–Wallis test, NIHSS: National Institutes of Health Stroke Scale, FAR: Fibrinogen-to-albumin ratio, min: Minimum, max: Maximum

Table 6. Distribution of FAR, fibrinogen, and albumin values according to the TOAST classification

Parameters	Large atherosclerotic n = 20 median (min–max)	Cardioembolic n = 10 median (min–max)	Lacunar n = 21 median (min–max)	*P* value*
FAR	10.42 (6.45–124.33)	9.32 (5.36–15.68)	11.66 (5.29–24.43)	0.205*
Fibrinogen	363.50 (229–493)	315.50 (243–409)	394 (201.70–853)	0.250*
Albumin	33.65 (3–39.10)	37.30 (25–45.36)	34 (21.8–43)	0.179*

*Kruskal–Wallis test, FAR: Fibrinogen-to-albumin ratio, min: Minimum, max: Maximum

Table 7. Distribution of patient fibrinogen, albumin, and FAR values according to hospitalization duration <1 week and >1 week

Parameters	Hospitalization duration <1 week median (min–max)	Hospitalization duration >1 week median (min–max)	*P* value*
FAR	10.41 (5.29–124.33)	10.71 (5.36–106.58)	0.549*
Fibrinogen	351 (201.7–853)	354 (229–604)	0.890*
Albumin	34.90 (3–43)	32.60 (3–45.36)	0.143*

*Mann–Whitney U test, FAR: Fibrinogen-to-albumin ratio, min: Minimum, max: Maximum

and ischemic stroke severity. We found that chronic diseases or smoking habits were unrelated to FAR values, fibrinogen, albumin, D-dimer, and CRP levels at admission in patients with ischemic stroke. Although the NIHSS scores were higher in smokers than in non-smokers, the difference was non-significant. Smoking was previously associated with increased levels of fibrinogen (24), and it is a considerable risk factor for ischemic stroke and its severity (25). However, our study population was not large enough to reach a precise conclusion regarding the effect of smoking.

According to the TOAST classification, the FAR values, fibrinogen levels, and albumin levels were not significantly different between stroke subgroups. The relationship between fibrinogen and ischemic stroke subgroups was inconsistent in some previous studies, and some current studies suggest that fibrinogen might not be useful for identifying the etiological sub-types of acute ischemic stroke (26,27). However, Peycheva et al. (19) demonstrated that an atherosclerotic stroke group had higher fibrinogen levels, and Jood et al. (28) revealed that large artery atherosclerosis and cardioembolic stroke groups had higher mean fibrinogen levels. The relationship between stroke sub-type and albumin levels remains controversial, and some studies have suggested that there is no relationship between stroke sub-type and albumin levels (20). However, others have revealed that lower albumin levels are associated with cardioembolic stroke (29). In the current literature, there is no study investigating the possible association between FAR and sub-types of ischemic stroke. In this study, there was no relationship between stroke sub-type and fibrinogen levels, albumin levels, or FAR values. In terms of FAR values, serum albumin levels, and fibrinogen levels, there were no significant differences between patients hospitalized longer than 1 week and other patients, indicating a lack of effect on disease severity based on NIHSS scores.

The FAR values were not associated with poor functional outcomes according to mRS scores. Rasyid et al. indicated that a higher fibrinogen level was a risk factor for a higher NIHSS score at the end of the first week and higher mRS score at the end of the 1-month follow-up (30). In addition, many studies have demonstrated that a high fibrinogen level could be a diagnostic marker for ischemic stroke and an indicator of poor prognosis both in the short and long term (19,31). Moreover, in previous research, lower albumin levels were related to poor functional outcomes (29,30,31,32). Dziedzic et al. (33) revealed that lower serum albumin levels could be an independent predictor of poorer outcomes, according to the mRS score. However, there is no research in the current literature similar to this study, analyzing the possible association between FAR and functional outcomes of patients with ischemic stroke.

More effective parameters have been recently obtained through the proportional analysis of simple and inexpensive laboratory data to determine the early and long-term prognosis of chronic diseases. The most well-known and studied method is the neutrophil/lymphocyte ratio (NLR).

Researchers' curiosity to understand the severity and prognosis of the disease has led to the study of new and effective proportional biomarkers. Using parameters with opposing variability will strengthen their significance and effectiveness. An evaluation of the literature to select a new rational parameter guided the choice of the FAR. Separate studies have demonstrated that fibrinogen and albumin could be associated with thrombotic and inflammatory diseases. This study aimed to investigate the relationship of FAR, based on the proportional calculation of fibrinogen and albumin, as in NLR, with ischemic stroke.

Recently, many studies have been conducted with the hypothesis that FAR, a computational marker, could be used to form the relationship more specifically between albumin and fibrinogen in diseases and may be useful in many pro-thrombotic and pro-inflammatory diseases. It is possible that FAR could be a valuable diagnostic tool for acute ischemic stroke with its effectiveness, ease, simplicity, and rapidity but not for the severity and prognosis of acute ischemic stroke. Currently, no studies have revealed the relationship between FAR and ischemic stroke severity and sub-types. This study provides a significant contribution to the literature on this subject.

Study Limitations

The study's limitations are that the relationship between infarct volume and FAR values was not examined and the number of cases was limited to sub-types based on severity and etiology. However, thrombolytic treatment can affect disease severity, and many cases in this study used this treatment, which could have affected the results. Additionally, this study only involved a small group of patients with ischemic stroke. New studies with a greater number of cases are needed to explore the results further.

Conclusion

The FAR is a novel rational diagnostic parameter of ischemic stroke and a more sensitive and specific marker than albumin and fibrinogen. However, it was not able to identify stroke severity and sub-types. The results, consisting of a limited number of patients, could form the basis of more extensive studies regarding FAR and ischemic stroke.

Ethics

Ethics Committee Approval: Ethical committee approval (decision date: August 01, 2021, number: 47674) for this study

was obtained from the Sakarya University Faculty of Medicine Ethical Committee.

Informed Consent: Consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.K., S.S., Concept: S.S., D.K., Design: S.S., D.K., Data Collection or Processing: E.Ç., S.S., E.S.D., Analysis or Interpretation: M.A., S.S., Literature Search: S.S., E.Ç., Writing: S.S., D.K., M.A., E.Ç.

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