

KÖZLEMÉNY

**ORIGINAL ARTICLE** 

# Fibrinogen to albumin ratio's prognostic value in ischemic stroke patients who underwent mechanical thrombectomy

Derya OZDOGRU<sup>1</sup>, Onur Kadir UYSAL<sup>2</sup>, Miray ERDEM<sup>1</sup>, Elif Banu SOKER<sup>1</sup>, Ilker OZTURK<sup>1</sup>, Akkan AVCl<sup>3</sup>, Zulfikar ARLIER<sup>1</sup>

<sup>1</sup>Health Science University, Adana City Training and Research Hospital, Department of Neurology, Adana, Turkey

<sup>2</sup>Health Science University, Adana City Training and Research Hospital, Department of Cardiology, Adana, Turkey

<sup>3</sup>Adana City Research and Training Hospital, Department of Emergency Medicine, Adana, Turkey

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## Correspondent:

Akkan AVCI, Ass. Prof., Health Science University, Adana City Research and Training Hospital, Department of Emergency Medicine, 01060, Adana, Turkey e-mail: drakkanavci@gmail.com gsm: +90533 423 03 69 https://0000-0002-4627-0909

## Érkezett:

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Background and purpose - Fibrinogen to albumin ratio (FAR) is thought to have a predictive effect in diseases such as cancer and myocardial infarction. We aimed to elucidate the prognostic value of FAR in ischemic stroke patients who underwent mechanical thrombectomy.

Methods - A total of 103 patients hospitalized for acute stroke who underwent mechanical thrombectomy within 6 hours of symptoms' outset have been analyzed retrospectively. Stroke severity was interpreted via the National Institutes of Health Stroke Scale (NIHSS) score during the neurological examination. Recanalization success after mechanical thrombectomy was evaluated with the TICI score (Thrombolysis in Cerebral Infarction scale), and 2b - 3 patients were recorded as those with recanalization. The patients' modified Rankin scale (mRS) at discharge and at the end of the third month were recorded.

**Results** – Statistically significant differences were observed in age, admission blood glucose, glomerular filtration rate and FAR according to the mRS scores of the patients in the third month (p<0.05). Significant variables in the risk factor analysis were re-evaluated in the multivariate model. The best model was determined using the backward Wald method in the multivariate model. A fibrinogén-albumin arány prognosztikai értéke mechanikus thrombectomián átesett ischaemiás stroke-os betegeknél Ozdogru D, MD; Uysal OK, Ass. Prof.; Erdem M, MD; Soker EB, MD; Avci A, Ass. Prof.; Arlier Z, MD, PhD

Háttér és cél – A fibrinogén-albumin arány (FAR) feltételezhetően prognosztikus értékű olyan betegségeknél, mint a rák és a szívinfarktus. Célunk a FAR prognosztikus értékének tisztázása volt olyan ischaemiás stroke-os betegeknél, akik mechanikus thrombectomián estek át.

Módszerek – 103 olyan, akut stroke miatt kórházba került beteg adatait elemeztük retrospektív módon, akiknél a tünetek megjelenésétől számított 6 órán belül mechanikus thrombectomiát végeztek. A stroke súlyosságát a neurológiai vizsgálat során a National Institutes of Health Stroke Skála (NIHSS-) pontszámokon keresztül értékeltük. A mechanikus thrombectomia utáni rekanalizációs sikert a TICI-pontszámmal (Thrombolysis in Cerebral Infarction scale) értékeltük, és a 2b-3 pontszámú betegeket sikeres rekanalizációval rendelkezőként azonosítottuk. A betegek módosított Rankinskála- (mRS-) pontszámát a hazabocsátáskor és a harmadik hónap végén rögzítettük. **Eredmények** – Statisztikailag szignifikáns

különbségeket figyeltünk meg az életkor, a kórházba történő felvételkor mért vércukorszint, a glomerularis filtrációs ráta és a FAR tekintetében a betegek harmadik hónap végén mért mRS-pontszámai szerint (p < 0,05). A rizikófaktor-elemzésben szignifikáns változókat újraértékeltük többváltozós modellben. and it was determined that differences in age, admission blood glucose, and FAR were significant.

Conclusion - FAR can be used as a novel, effective, economical, and practical biomarker in patient with acute ischemic stroke who underwent mechanical thrombectomy.

**Keywords**: fibrinogen to albumin ratio, ischemia, stroke, cerebral infarction, thrombectomy

A legjobb modellt a többváltozós modellben a backward Wald-módszerrel határoztuk meg, és megállapítottuk, hogy az életkor, a felvételi vércukorszint és a FAR különbségei szignifikánsak.

Következtetés – A FAR új, hatékony, gazdaságos és praktikus biomarkerként használható a mechanikus thrombectomián átesett akut ischaemiás stroke-os betegeknél.

Kulcsszavak: fibrinogén-albumin arány, ischaemia, stroke, cerebralis infarktus, thrombectomia

librinogen is the most common plasma coagulation  $\Gamma$  factor and is considered as an acute-phase reactant protein that is positively correlated with inflammation. Fibrinogen is initially synthesized in the liver, participates in various physiological processes after bleeding, and is a marker of pathological inflammation<sup>1</sup>.

Studies have shown that plasma fibrinogen levels rise in chronic and acute ischemic stroke; thus, it can be considered a solid and independent marker of myocardial infarction, stroke, and atherothrombotic events<sup>2</sup>. On the other hand, albumin is an acute-phase protein with anti-inflammatory properties and inhibitory effects on platelet aggregation and thrombus formation. It is the most abundant plasma protein and is an anti-inflammatory marker. Studies in the literature report that albumin levels decrease in conditions such as subarachnoid and cerebral haemorrhages, venous thromboembolism, and other ischemic events3. Low albumin levels are generally accepted as predictor of poor prognosis in ischemic stroke4.

The fibrinogen-to-albumin (FAR) ratio has been scrutinized for its predictive value in diseases, such as cancer and myocardial infarction. In patients with acute ischemic stroke, a high FAR is more sensitive and specific than fibrinogen alone as it indicates hypercoagulability and inflammation progression<sup>5</sup>. Moreover, the specificity and sensitivity of FAR is higher than fibrinogen alone with regard to anticipating the severity of chronic venous insufficiency, an advanced inflammatory disease6.

This research aimed to elucidate the prognostic value of FAR for ischemic stroke patients who underwent mechanical thrombectomy. The study investigated the prognostic value of FAR concerning the mortality and disability status of the patients. The central question guiding this research was: 'Can the ratio of fibrinogen to albumin be used to decide the prognosis of ischemic stroke patients who underwent mechanical thrombectomy?'

# Materials and method

A total of 103 acute stroke patients were treated at our institution's neurology stroke clinic from January 2022 to December 2022. Those patients who underwent mechanical thrombectomy within the first 6 hours of symptom onset were analyzed retrospectively. The decision for mechanical thrombectomy when treating these patients was made according to the guidelines of the American Heart Association/American Stroke Association 20197. Accordingly, patients were evaluated using the Alberta stroke program early computed tomography score  $(ASPECTS) \ge 6$ , the National Institute of Health Stroke Scale (NIHSS)  $\geq$  6, and according to the large or medium vessel occlusion. Basically, two methods in mechanical thrombectomy were used. The first procedure was a stent-retriever thrombectomy based on retractable stents and thrombo-aspiration (ADAPT) with large catheters. Combined methods were used in other cases. The method to be applied was chosen according to the patient's characteristics during the procedure.

All procedures were in compliance with the ethical regulations of the relevant committee on human experimentation (both institutional and national) and with the revised version (2018) of WMA Helsinki Declaration in 1975. The ethics committee of our institution granted approval on 02/02/2023 with protocol number 2398. Since this research was a retrospective study, participants' consents were not included in the study.

Demographic characteristics of the patients, outcome of neurological examinations, time to mechanical thrombectomy, treatment characteristics, recanalization time, and data of symptomatic intracranial bleedings after the procedure were recorded. The severity of the stroke was interpreted via the NIHSS score during the neurological examination. Recanalization success after mechanical thrombectomy was evaluated using the Thrombolysis in Cerebral Infarction scale (TICI) score, and 2b-3 patients were recorded as those with recanalization. The patients' modified Rankin scale (mRS) at discharge and at the end of the third month were recorded. Those with mRS 0-2 had recorded as to have good clinical outcomes, while those with scores  $\geq 3$  as to have poor outcomes.

Blood samples were evaluated at the time of hospital admission. C-reactive protein (CRP) levels and neutrophil/lymphocyte, neutrophil/platelet, platelet/lymphocyte, and fibrinogen/albümin ratios were evaluated as inflammatory biomarkers.

Patients who received intravenous or intra-arterial thrombolytic therapy, patients with active infections on the day of hospitalization, those with a diagnosis of malignancy, and those with chronic kidney failure, chronic liver failure, and blood diseases were excluded from the analysis. Patients receiving thrombolytic therapy were excluded because it might have interfered with fibrinogen metabolism; only patients who underwent mechanical thrombectomy were analysed.

## Statistical analysis

Patients' data were assessed with IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 (IBM Corp., Armonk, NY) package program. For categorical data, frequency and percentage were stored, whereas mean  $\pm$  standard deviation, and median, minimum, and maximum descriptive values were measured for continuous data. The Kolmogorov-Smirnov test was used to determine the normality of the data. In the comparisons between the groups, the Independent Sample T-Test was used for those with normal distribution for the two groups, the Mann Whitney-U Test for those who did not show normal distribution, and the Fisher's Exact or Chi-Squared Test was used for the comparison of categorical variables. Logistic Regression Analysis was also used to analyze risk factors. In the risk factor analysis, the variables were evaluated in univariate analysis. The variables found to be significant were re-evaluated in the multivariate model, and the best model was determined with the retrospective Wald method. The results were considered statistically significant when the p-value waas < 0.05.

**Table 1.** Distribution of demographic and clinical characteristics of

(N=103)	n (%)	Mean±SD	Median (Min-Max)
Gender			
Woman	51 (49.5)		
Male	52 (50.5)		
BMI (kg/m²)		26.8±4	26.1 (17.6-40.4)
Age (years)		67±11	68 (40-91)
HT	97 (94.2)		
Hyperlipidemia	19 (18.4)		
DM	56 (54.4)		
CAD	35 (34)		
AF	32 (31.1)		
CHF	19 (18.4)		
Cardiac mechanical valve	9 (8.7)		
Obesity	13 (12.6)		
Cigarette	23 (22.3)		
CKD	15 (14.6)		
NIHSS arrival		18.4±3.4	19 (6-26)
Tandem occlusion	15 (14.6)		
ICA occlusion	27 (26.2)		
MCA M1 occlusion	50 (48.5)		
PCA occlusion	1 (1)		
Basilar occlusion	5 (4.9)		
MCA M2 occlusion	5 (4.9)		
Stent retriever	53 (51.5)		
Symptom onset (min)		141.4±81.8	122 (30-396)
Imaging time (min) (computed tomog- raphy)		14.1±6.4	12 (5-36)
ASPECTS		9±0.9	9 (7-10)
Door crotch time (min)		48.8±19.3	55 (12-76)
Recanalization time (min)		56.1±15.3	57 (15-94)
TICI score			
2b-3	87 (84.5)		
0-2a	16 (15.5)		
NIHSS score 24. Hours		12.2±7.4	11 (0-26)
Symptomatic intracra- nial hemorrhage	13 (12.6)		
Brain edema	22 (21.4)		
NIHSS discharge		5.7±4.9	4 (0-20)

Table 1 continues on the next page.

Continuation of Table 1.

(N=103)	n (%)	Mean±SD	Median (Min-Max)
mRS discharge		3.1±2.2	4 (0-6)
mRS 3rd month		2.9±2.4	3 (0-6)
Mortality	28 (27.2)		
TOAST			
Atherothrombotic	51 (49.5)		
Cardioembolic	46 (44.7)		
Other	1 (1)		
Cryptogenic	5 (4.9)		

BMI: body mass index, HT: hypertension, DM: diabetes mellitus, CAD: coronary artery disease, AF: atrial fibrillation, CHF: congestive heart failure, CKD: chronic kidney disease, NIHSS: National Institutes Of Health Stroke Scale, ICA: internal carotid artery, MCA: middle cerebral artery, PCA: posterior cerebral artery, ASPECTS: Alberta stroke program early computed tomography score, TICI: thrombolysis in cerebral infarction scale, mRS: modified Rankin scale, TOAST: Trial of Org 10172 in acute stroke treatment

# Results

This study included 103 patients with a mean age of 67  $\pm$  11 years (age range: 40–91 years), out of whom 52 (50.5 %) were male.

The distribution of demographic and clinical findings of the patients (Table 1) according to their mRS scores at three months is given in Table 2. The mean age was 64  $\pm$  12 years in the mRS 0-2 group and 71  $\pm$  9 years in the mRS 3-6 group. A statistically significant difference was observed in terms of age (p = 0.001). Admission blood glucose (BG) was  $124.1 \pm 44.7$  in the mRS 0-2 group and  $154.3 \pm 54$  in the mRS 3-6 group; admission BG in the mRS 3-6 group was statistically significantly higher (p < 0.001). Glomerular filtration rate (GFR) was  $87.6 \pm 20.6$  in the mRS 0-2 group and  $74.8 \pm 21.1$  in the mRS 3-6 group; GFR in the mRS 3–6 group was statistically significantly higher (p = 0.003). The FAR ratio was calculated as 0.082  $\pm 0.029$  in the mRS 0-2 group and 0.094  $\pm 0.027$  in the mRS 3-6 group, and the FAR ratio in the mRS 3-6 group was statistically significantly higher (p = 0.024).

The results of the logistic regression analysis concerning the risk of poor clinical outcome at three months are given in **Table 3**. The variables found to be significant in **Table 2** in the risk factor analysis were first univariate after which significant variables in the risk factor analysis were re-evaluated using a multivariate model. The best model was determined using the backward Wald method in the multivariate model. When all significant variables were re-evaluated in multivariate analysis, it was determined that differences in age (OR=1.083), admission BG (OR=1.016), and fibrinogen/albumin ratio (OR=1.247) were significant.

## Discussion

The study found that the difference in FAR was significant in patients who underwent mechanical thrombectomy for ischemic stroke, especially regarding clinical improvement at the three-month mark.

Inflammation plays a significant role in ischemic stroke and cerebral haemorrhage. The FAR has been defined in numerous studies as an indicator of unfavourable consequences and detrimental effects regarding patients' suffering from sepsis, cancer, cardiovascular diseases, and stroke2. Fibringen has a role in the coagulation system and is an important reference point for continuous inflammation<sup>8, 9</sup>. Interactions of fibrinogen with endothelial cells, platelets, monocytes, and lymphocytes facilitate an increase in the potential of inflammatory response in atherosclerosis, causing thrombosis, vascular endothelial damage,

and hemorheological disorders<sup>10</sup>. Moreover, fibrinogen impacts the nervous system with a role in neuronal injury, neuroinflammation, and immune cell recruitment<sup>11</sup>. Fibrinogen binds to microglial receptors, stimulates the secretion of proinflammatory cytokines and chemokines, and leads to the release of reactive oxygen species related to brain injury<sup>12, 13</sup>. According to several studies, the administration of fibrinogen-depleting agents to patients with acute ischemic stroke may lessen neurological disability<sup>14, 15</sup>. In acute stroke, elevation of acute phase reactants lasts for a very short time and ends within 24 h<sup>16</sup>. In addition, it is thought that the change in these factors is not the result but rather the cause of acute stroke and the low-intensity intravascular coagulation that is present in stroke<sup>17</sup>. Increased plasma levels of fibrinogen, which also has an important role in coagulation, have been found to be associated with atherosclerosis in coronary, cerebral, and peripheral arteries. An increase in fibrinogen leads to platelet aggregation, thrombus formation, and an increase in blood viscosity<sup>18</sup>. Some studies have reported a possible, mild increase in acute-phase reactants in atherosclerotic vascular disease due to underlying chronic inflammation, a factor that may determine the patient's prognosis<sup>19, 20</sup>. It has been suggested that prognosis in patients with stroke may be related to acute phase reactants. However, studies in the literature also report that acute phase reactants are not determinative for survival and prognosis in stroke<sup>21, 22</sup>. Although atherosclerosis causes a chronic acute phase response, an acute increase in this value after a stroke occurs. These values may help to determine the prognosis. However, more detailed and controlled studies with many patient groups are required to decide on the usefulness of using acute-phase reactants.

**Table 2.** Distribution of demographic and clinical findings of the patients by third month mRS status

	mRS Third Month						
	0-1-2			>2			p-
	n (%)	Mean±SD	Median (Min-Max)	n (%)	Mean±SD	Median (Min-Max)	value
Gender							0.370
Woman	21 (43.8)			30 (54.5)			
Male	27 (56.3)			25 (45.5)	,		
BMI (kg/m²)		26.4±3.1	26.1 (20.8-36.1)		27.2±4.7	26.2 (17.6-40.4)	0.539ª
Age (years)		64±12	65 (40-91)		71±9	72 (43-85)	0.001 <sup>b</sup>
HT	45 (93.8)			52 (94.5)			1.000
Hyperlipidemia	8 (16.7)			11 (20)			0.857
DM	22 (45.8)			34 (61.8)			0.154
CAH	18 (37.5)			17 (30.9)			0.620
AF	14 (29.2)			18 (32.7)			0.860
CHF	7 (14.6)			12 (21.8)			0.490
Cardiac mechanical valve	6 (12.5)			3 (5.5)			0.298
Obesity	4 (8.3)			9 (16.4)			0.354
Smoking	12 (25)			11 (20)			0.711
CKD	3 (6.3)			12 (21.8)	,		0.051
Occluded vessels							0.101
Tandem occlusion	9 (18.8)			6 (10.9)			
ICA occlusion	11 (22.9)			16 (29.1)			
MCA M1 occlusion	23 (47.9)			27 (49.1)			
PCA occlusion	1 (2.1)			0 (0)			
Basilar occlusion	0 (0)			5 (9.1)			
MCA M2 occlusion	4 (8.3)			1 (1.8)			
Stent retriever	22 (45.8)			31 (56.4)			0.385
Symptom duration (min)		129.9±78.2	119 (30-385.1)		151.4±84.2	138 (30-396)	0.126ª
Imaging time (min) (computed tomog- raphy)		14.2±7.4	12 (6-36)		13.9±5.6	14 (5-25)	0.751ª
Door crotch time (min)		46.7±20.2	53.5 (15-76)		50.6±18.6	58 (12-72)	0.475ª
Recanalization time (min)		53.4±15.4	56.5 (15-78)		58.5±15	59 (25-94)	0.093 <sup>b</sup>
TOAST							0.619
Atherothrombotic	22 (45.8)			29 (52.7)			
Cardioembolic	22 (45,8)			24 (43,6)			
Other	1 (2.1)			0 (0)	,		
Crptogenic	3 (6.3)			2 (3.6)			
Admission blood glucose (mg/dl)		124.1±44.7	106.5 (81-263)		154.3±54	142 (90-282)	<0.001°

Table 2 continues on the next page.

#### Continuation of Table 2.

#### mRS Third Month

		14 111011611					
	0-1-2 >2				p-		
	n (%)	Mean±SD	Median (Min-Max)	n (%)	Mean±SD	Median (Min-Max)	value
WBC (10³/µl)		10.5±3.4	10.5 (1.2-20.7)		10.6±4.1	10.3 (3.6-23)	0.886 <sup>b</sup>
LY (10 <sup>3</sup> /μl)		1.8±0.9	1.7 (0.5-4.1)		1.8±1.1	1.5 (0.6-4.6)	0.401a
NE (10³/µl)		7.7±3.1	7.4 (0.4- 16.9)		8±4.1	7.2 (0.6-20.1)	0.992ª
HGB (g/dl)		12.6±2	12.8 (7.8-16.6)		12.4±2	12.5 (7-15.6)	0.664 <sup>b</sup>
HTC (%)		38±5.1	38.4 (26.3-49.3)		37.4±5.6	38.2 (20.2-45.4)	0.603b
MPV (fL)		9.2±1.1	9 (7.3-12.3)		9.3±0.9	9.2 (7.5-11.4)	0.457ª
PLT (10³/µl)		256.9±93.1	237 (123-552)		252±94.9	232 (114-668)	0.882ª
MCV (fL)		86.9±6.9	87.7 (61.7-104.1)		85.2±9.1	85.1 (67.7-113.1)	0.192ª
RDW (%)		15.2±2.2	14.6 (12.4-22.4)		15.2±2.1	14.3 (12.5-21.1)	0.968ª
GFR (ml/min/1.73 m²)		87.6±20.6	91.5 (29-130)		74.8±21.1	78 (26-117)	0.003 <sup>b</sup>
Urea (mg/dl)		36.4±12	32.5 (16-68)		42.7±18.2	38 (20-117)	0.073ª
Creatinine (mg/dl)		0.8±0.2	0.8 (0.4-1.7)		0.9±0.3	0.9 (0.5-1.9)	0.139ª
Triglyceride (mg/dl)		107.7±80.8	76 (32-438)		110.1±54.1	91 (44-287)	0.101a
LDL (mg/dl)		121.9±32.6	120.5 (52-204)		123.6±36	123 (58-248)	0.794 <sup>b</sup>
HDL (mg/dl)		46.6±14.3	44 (20-92)		45.3±12.3	43 (24-78)	0.641a
CRP (mg/L)		13.7±22.9	5 (0.5-91.4)		16.4±25	7 (0.8-131)	0.098a
Troponin (ng/L)		19.9±47.4	8 (2-321)		37.8±83.3	12 (2-415)	0.145ª
Fibrinogen/Albumin ratio (g/L / g/L)		0.082±0.029	0.074 (0.038-0.191)		0.094±0.027	0.091 (0.043-0.174)	0.024 <sup>b</sup>
NE/LY ratio		5.5±4.2	4.2 (0.8- 20.8)		6.6±5.2	6 (0.2-23.3)	0.399ª
NE/PLT ratio		0.03±0.01	0.03 (0-0.08)		0.03±0.02	0.03 (0-0.09)	0.848a
PLT/LY ratio		181.4±133.8	133.3 (56.4-791.7)		201.2±148.5	175.7 (35.2-742.2)	0.583ª

a: Mann Whitney U Test; b: Independent T Test.

BMI: body mass index, HT: hypertension, DM: diabetes mellitus, CAD: coronary artery disease, AF: atrial fibrillation, CHF: congestive heart failure, CKD: chronic kidney disease, ICA: internal carotid artery, MCA: middle cerebral artery, PCA: posterior cerebral artery, mRS: modified rankin scale, TOAST: Trial of Org 10172 in acute stroke treatment, WBC: white blood cell, LY: lymphocyte, NE: neutrophil, HGB: hemoglobin, HTC: hematocrit, MPV: mean platelet volume, PLT: platelet, MCV: mean corpuscular volume, RDW: red cell distribution width, GFR: glomerular filtration rate, LDL: low-density lipoprotein, HDL: high-density lipoprotein, CRP: C-reactive protein

**Table 3.** Evaluation of risk factors affecting poor clinical outcome at 3 months in patients

	Multivariate Analysis*		
	OR (95% CI)	p-value	
Age	1.083 (1.033-1.136)	0.001	
Admission blood glucose (mg/dl)	1.016 (1.005-1.026)	0.004	
GFR (ml/min/1.73 m <sup>2</sup> )	0.99 (0.97-1.02)	0.74	
Fibrinogen Albumin Ratio	1.247 (1.036-1.501)	0.020	

<sup>\*</sup> Backward wald method. GFR: glomerular filtration rate

As a negative acute-phase protein, albumin exhibits neuroprotective effects and is an important clinical parameter for liver function. Some studies have shown that albumin reduces blood-brain barrier permeability, brain oedema, and infarct volume<sup>23, 24</sup>. Albumin may provide neuroprotection through its antioxidant and anti-inflammatory activities and regulation of microvascular permeability<sup>24</sup>. Albumin inhibits platelet aggregation, has antioxidant functions, and is inversely associated with inflammation<sup>25, 26</sup>. Decreased albumin levels stimulate lipid and coagulation synthesis and promote atherosclerotic plaques and thrombosis with hyperlipidaemia and hypercoagulability. It has also been shown that albumin has neuroprotective functions in patients and improves functional outcomes in stroke by reducing neurotoxicity<sup>27, 28</sup>. Low serum albumin levels have been associated with higher mortality risk in patients with cerebral haemorrhage<sup>29</sup>. FAR has recently been associated with worse survival and a higher risk of recurrence in various malignancies, such as hepatocellular, gastric, and non-small cell lung cancers<sup>30</sup>. FAR is associated with inflammation and has proven to be an encouraging indicator for disease progression and for unfavourable long-term prognosis in patients with coronary artery disease and stroke<sup>31, 32</sup>. The fibrinogen-to-albumin ratio may help to detect patients with high risks of in-hospital mortality at early stages, to monitor the prognosis, and determine intensive care unit (ICU) treatment<sup>33</sup>.

FAR may be associated with ischemic events through two mechanisms: 1) fibrinogen facilitates the release of proinflammatory cytokines, such as interleukin-1 and tumour necrosis factor<sup>34, 35</sup> and 2) serum albumin also takes part in acute inflammatory reactions while serving as a negative inflammatory protein with protective anti-inflammatory properties<sup>36</sup>. Therefore, a high FAR leads to an increase in the risk of ischemic events.

Haemorrhagic transformation and the subsequent inflammatory responses are significant risk factors for stroke. Ruan et al.37 conducted a study on 256 stroke patients and found that FAR was independently associated with an increased risk of haemorrhagic transformation after acute ischemic stroke. Castellanos et al.38 described a link between a positive outcome and low fibrinogen levels in the case of non-surgical patients with moderate to large spontaneous intracerebral haemorrhage (ICH).

As verified in several studies, FAR forecasts that intracerebral infarction occurs and prognoses. Acharya et al. (2020) indicated that an increased level of FAR was strongly related to a higher prospect of acute cerebral infarction on the initial day

of extracorporeal membrane oxygenation<sup>32</sup>. In addition, Zheng et al.<sup>39</sup> recently reported the association of FAR with severity and stated that patients diagnosed with acute lacunar cerebral infarction have worse three-month outcomes.

Zhai et al. (2022) suggested that FAR was related to three months of poor clinical outcomes in acute pons infarction and even illustrated a positive correlation of FAR with the baseline NIHSS in conjunction with the mRS scores. Even though infarct sizes did not differ remarkably among the high and low levels of FAR groups, the high FAR group had larger infarct sizes, that involved more fibre bundles of the pons and the corticospinal tract in the basal pons nucleus, in particular. In conclusion, the baseline NIHSS scores of the high level FAR group were comparatively greater and led to worse outcomes. The given results firmly underpins the prognosis of this indicator for the short-term effect of severe pons infarction<sup>40</sup>. This analysis also suggested that a statistically meaningful difference between the patients' FAR and mRS scores at the three-month mark could be found. Furthermore, multivariate analysis demonstrated that the difference in FAR was significant.

Using FAR has certain advantages. First, FAR is not affected by interventions in ICH patients. Moreover, obtaining fibringen and albumin and calculating their ratio from regular blood samples taken upon admission is straightforward. In contrast, alternative methods, such as the NIHSS or APACHE II score or calculating the ICH volume, are time-consuming and require more focused attention<sup>41–43</sup>. Last, FAR is a relatively inexpensive assessment tool for use in the healthcare system. Nonetheless, it should not be regarded as the sole indicator of death<sup>44</sup>. On the other hand, when combined with prominent predictors, FAR appears to be a novel parameter to ameliorate ICU treatment and to identify patients with high risks of in-hospital mortality in advance<sup>5</sup>.

In patients undergoing mechanical thrombectomy, many prognostic factors such as age, recanalisation time,

accompanying comorbidities, and brain collateral status of the patient are present. The association of high blood glucose and renal dysfunction with poor functional outcomes in mechanical thrombectomy has been shown in many studies, and studies on biomarkers with prognostic value are ongoing<sup>46-48</sup>. Advanced age and high glucose levels have negative effect on clinical outcomes. In a study, every 10 years of age increase was associated with a 3.6-fold decrease in good clinical outcome, and every 20 mg/dL increase in blood glucose values was associated with a 1.43-fold decrease in good clinical outcome<sup>49</sup>. In a multicentre study, good clinical outcome was observed in 60% of patients aged 18-56 years, whereas good clinical outcome was found in only 37% of patients aged 69-76 years<sup>50</sup>. Impaired collateral circulation, higher prevalence of comorbid conditions, post-stroke medical complications and difficult vascular anatomy may be responsible for the decreased functional outcome at older age. Elevated admission blood glucose and a history of diabetes mellitus have been associated with increased infarct volume and increased intracranial bleeding despite recanalisation<sup>51, 52</sup>. This condition has been associated with hyperglycaemia and blood brain barrier disruption, mitochondrial dysfunction and endothelial cell apoptosis<sup>52, 53</sup>. In addition, lactic acid accumulation may lead to increased intracellular acidosis and ischaemic damage<sup>54</sup>. In our study, advanced age and admission blood glucose were found to be independent risk factors for poor clinical outcome at 3 months. In studies, low GFR has been shown to be associated with poor functional outcome, haemorrhagic transformation and increased mortality rates<sup>55, 56</sup>. Low GFR may be associated with the presence of a history of vascular comorbidities such as hypertension, diabetes mellitus, atrial fibrillation, ischaemic heart disease that may lead to renal dysfunction and

may explain why these patients have poor clinical outcome<sup>56</sup>. Studies have suggested that not low GFR but concomitant proteinuria or albuminuria is an independent determinant of poor functional outcome in patients with ischaemic stroke<sup>57, 58</sup>.

## Conclusion

As demonstrated also in the literature, the FAR value can be utilized as a prognostic factor for patients with cardiovascular diseases, cancers, ischemic stroke, and intracerebral haemorrhage, with an increase in the FAR value indicating a micro-inflammatory condition. Moreover, FAR can serve as a recent, effective, economical, and practical instrument in patients with serious ischemic stroke who underwent mechanical thrombectomy.

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# References

- 1. Prasad MK, Marandi S, Mishra B, Guria RT, Kumar A, et al. Association of fibrinogen with 1schemic stroke: A systematic review and meta-analysis. Cureus 2023;15(1):e34335. https://doi.org/10.7759/cureus.34335
- 2. Surma S, Banach M. Fibrinogen and atherosclerotic cardiovascular diseases-review of the literature and clinical studies. Int J Mol Sci 2022;23:193. https://doi.org/10.3390/ijms23010193
- 3. Wang A, Zhang Y, Xia G, Tian X, Zuo Y, Chen P, et al. Association of serum albumin to globulin ratio with outcomes in acute ischemic stroke. CNS Neurosci Ther 2023;29(5):1357-67. https://doi.org/10.1111/cns.14108
- 4. Mangoni AA, Zinellu A. A systematic review and meta-analysis of serum concentrations of ischaemia-modified albumin in acute ischaemic stroke, intracerebral haemorrhage, and subarachnoid haemorrhage. Biomolecules 2022;12(5):653. https://doi.org/10.3390/biom12050653
- 5. Yang M, Tang L, Bing S, Tang X. Association between fibrinogento-albumin ratio and hemorrhagic transformation after intravenous thrombolysis in ischemic stroke patients. Neurol Sci 2023;44(4):1281-8.
  - https://doi.org/10.1007/s10072-022-06544-4
- 6. Bender M, Haferkorn K, Tajmiri-Gondai S, Uhl E, Stein M. Fibrinogen to albumin ratio as early serum biomarker for predic-

- tion of intra-hospital mortality in neurosurgical intensive care unit patients with spontaneous intracerebral hemorrhage. J Clin Med 2022;11(14):4214. https://doi.org/10.3390/jcm11144214
- 7. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of
- patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke 2019;50: e344-e418. https://doi.org/10.1161/STR.00000000000000211
- 8. Magid-Bernstein J, Girard R, Polster S, Srinath A, Romanos S, Awad IA, Sansing LH. Cerebral hemorrhage: Pathophysiology, treatment, and future directions. Circ Res 2022:130(8):1204-29. https://doi.org/10.1161/CIRCRESAHA.121.319949
- Sheth KN. Spontaneous Intracerebral Hemorrhage. N Engl J Med 2022;387(17):1589-96. https://doi.org/10.1056/NEJMra2201449
- 10. Guo YH, Hernandez I, Isermann B, et al. Caveolin-1-dependent apoptosis induced by fibrin degradation products. Blood 2009;113(18):4431-9. https://doi.org/10.1182/blood-2008-07-169433
- 11. Merlini M, Rafalski VA, Rios PE, et al. Fibrinogen induces microglia-mediated spine elimination and cognitive impairment in an Alzheimer's disease model. Neuron 2019;101(6):1099-08.e6. https://doi.org/10.1016/j.neuron.2019.01.014
- 12. Lominadze D, Dean WL, Tyagi SC, et al. Mechanisms of fibrinogeninduced microvascular dysfunction during cardiovascular disease. Acta Physiologica (Oxford, England) 2019;198(1):1-13. https://doi.org/10.1111/j.1748-1716.2009.02037.x
- 13. Petersen MA, Ryu JK, Akassoglou K. Fibrinogen in neurological diseases: Mechanisms, imaging and therapeutics. Nature Reviews. Neuroscience 2018;19(5):283-301. https://doi.org/10.1038/nrn.2018.13
- 14. Chen J, Sun D, Liu M, et al. Defibringen therapy for acute ischemic stroke: 1332 consecutive cases. Scientific Reports 2018;8(1):9489. https://doi.org/10.1038/s41598-018-27856-6
- 15. Guo Y, Zuo YF, Wang OZ, et al. Metaanalysis of defibrase in treatment of acute cerebral infarction. Chinese Medical Journal 2006;119(8):662-8. https://doi.org/10.1097/00029330-200604020-00010
- 16. Fon EA, Mackey A, Cote R, et al. Hemostatic markers in acute transient ischemic attacks. Stroke 1994;25:282-6. https://doi.org/10.1161/01.STR.25.2.282
- 17. Feinberg WM, Bruck DC, Ring ME, Corrigan JJ Jr. Hemostatic markers in acute ischemic stroke. Stroke 1989;20:592-7. https://doi.org/10.1161/01.STR.20.5.592
- 18. Mosesson MW. Fibrinogen and fibrin structure and functions. J Thromb Haemost 2005;3(8):1894-904. https://doi.org/10.1111/j.1538-7836.2005.01365.x
- 19. Gussekloo J, Schaap MCL, Frolich M, et al. C-reactive protein is a strong but nonspesific risk factor of fatal stroke in elderly persons. Arterioscler Thromb Vas C Biol 2000;20:1047-51. https://doi.org/10.1161/01.ATV.20.4.1047
- 20. Anuk T, Assayag EB, Rotstein R, et al. Prognostic implications of admission inflammatory profile in acute ischemic neurologica\ events. Acta Neurol Scand 2002;106:196-9. https://doi.org/10.1034/j.1600-0404.2002.01224.x
- 21. Canova CR, Courtin C, Reinhart WH. C-reactive protein in cerebrovascular events. Aterosclerosis 1999;147:49-53. https://doi.org/10.1016/S0021-9150(99)00162-8
- 22. Iyigün I, Bakirci Y. Plasma concentrations of C-reactive protein and fibrinogen in ischemic stroke. J Int Med Res 2002;30:591-6. https://doi.org/10.1177/147323000203000607
- 23. Belayev L, Liu Y, Zhao W, Busto R, Ginsberg MD. Human albümin therapy of acute ischemic stroke: Marked neuroprotective efficacy at moderate doses and with a broad therapeutic window. Stroke 2001;32(2):553-60. https://doi.org/10.1161/01.STR.32.2.553
- 24. Park H, Hong, M, Jhon G. J, Lee Y, Suh M. Repeated oral administration of human serum albumin protects from the cerebral ischemia in rat brain following MCAO. Experimental Neurobiology 2017;26(3):151-7. https://doi.org/10.5607/en.2017.26.3.151

- 25. Roche M, Rondeau P, Singh NR, et al. The antioxidant properties of serum albumin. FEBS Lett 2008;582(13):1783-7. https://doi.org/10.1016/j.febslet.2008.04.057
- 26. Rael LT. Leonard J. Salottolo K. et al. Plasma oxidized albumin in acute ischemic stroke is associated with better outcomes. Front Neurol 2019:10(709). https://doi.org/10.3389/fneur.2019.00709
- 27. Joles JA, Willekes-Koolschijn N, Koomans HA. Hypoalbuminemia causes high blood viscosity by increasing red cell lysophosphatidylcholine. Kidney Int 1997;52(3):761-70. https://doi.org/10.1038/ki.1997.393
- 28. Idicula TT, Waje-Andreassen U, Brogger J, et al. Serum albumin in ischemic stroke patients: the higher the better. The Bergen Stroke Study. Cerebrovasc Dis 2009;28(1):13-7. https://doi.org/10.1159/000215938
- Muhtaroğlu A, Çapoğlu R, Uygur FA, Harmantepe AT, Bayhan Z, Gönüllü E. FAR ratio as prognostic biomarker in AMI. SN Compr Clin Med 2023;5(1):109. https://doi.org/10.1007/s42399-023-01451-x
- 30. Chen J, Zeng Z, Fang Z, Ma F, Lv M, Zhang J. Risk factors for thrombolysis-related intracranial hemorrhage: a systematic review and meta-analysis. Thromb J 2023;21(1):27. https://doi.org/10.1186/s12959-023-00467-6
- 31. Çetin M, Erdoğan T, Kiriş T, Özer S, Yilmaz AS, Durak H, et al. (2019). Predictive value of fibrinogen-to-albumin ratio in acute coronary syndrome. Herz. https://doi.org/10.1007/s00059-019-4840-5
- 32. Acharya P, Jakobleff WA, Forest SJ, Chinnadurai T, Mellas N, Patel SR, et al. Fibrinogen albumin ratio and ischemic stroke during venoarterial extracorporeal membrane oxygenation. ASAIO J 2020;66(3):277-282. https://doi.org/10.1097/MAT.0000000000000992
- 33. Badr MY, Elkholy AA, Shoeib SM, Bahey MG, Mohamed EA, Reda AM. Assessment of incidence of cerebral vascular diseases and prediction of stroke risk in chronic obstructive pulmonary disease patients using multimodal biomarkers. Clin Respir J 2023; 17(3):211-28. https://doi.org/10.1111/crj.13587
- 34. Jensen T, Kierulf P, Sandset PM, et al. Fibrinogen and fibrin induce synthesis of proinflammatory cytokines from isolated peripheral blood mononuclear cells. Thromb Haemost 2007;97(5):822-9. https://doi.org/10.1160/TH07-01-0039
- 35. Yakovlev S, Zhang L, Ugarova T, Medved L. Interaction of fibrin(ogen) with leukocyte receptor alpha M beta 2 (Mac-1): further characterization and identification of a novel binding region within the central domain of the fibrinogen gamma-module. Biochemistry 2005;44(2):617-26. https://doi.org/10.1021/bi048266w
- 36. Chojkier M. Inhibition of albumin synthesis in chronic diseases: molecular mechanisms. J Clin Gastroenterol 2005;39(4 suppl 2): S143-S146.
- https://doi.org/10.1097/01.mcg.0000155514.17715.39 37. Ruan Y, Yuan C, Liu Y, Zeng Y, Cheng H, Cheng Q, et al. High fibrinogen-to-albumin ratio is associated with hemorrhagic transformation in acute ischemic stroke patients. Brain Behav 2021;11(1):e01855 https://doi.org/10.1002/brb3.1855
- 38. Castellanos M, Leira R, Tejada J, Gil-Peralta A, Dávalos A, Castillo J, Stroke Project, Cerebrovascular Diseases Group of the Spanish Neurological Society. Predictors of good outcome in medium to large spontaneous supratentorial intracerebral haemorrhages. J Neurol Neurosurg Psychiatry 2005;76(5):691-5. https://doi.org/10.1136/jnnp.2004.044347
- 39. Zheng L, Wang Z, Liu J, Yang X, Zhang S, Hao Z, Liu M, Wang D. Association between admission blood fibrinogen-to-albumin ratio and clinical outcomes after acute lacunar stroke. Biomark Med 2021;15(2):87-96. https://doi.org/10.2217/bmm-2019-0537
- 40. Zhai M, Cao S, Lu J, Xu H, Xia M, Li Z. The relationship between the fibrinogen to albumin ratio and early outcomes in patients with acute pontine infarction. Clin Appl Thromb Hemost 2022;28:10760296211067260. https://doi.org/10.1177/10760296211067260
- 41. Wang R, Li S, Hao L, Wang Z, Ge Z, Yang S. A meta-analysis of in-

- travenous thrombolysis versus bridging therapy for ischemic stroke. Medicine (Baltimore) 2022;101(39):e30879. https://doi.org/10.1097/MD.0000000000030879
- 42. Hendrix P. Melamed I. Collins M. Lieberman N. Sharma V. Goren O. et al. NIHSS 24 h after mechanical thrombectomy predicts 90-day functional outcome. Clin Neuroradiol 2022;32(2):401-6. https://doi.org/10.1007/s00062-021-01068-4
- 43. Wang L, Li G, Hao Y, Hao M, Xiong Y. Intravenous thrombolysis for mild stroke: NIHSS 3-5 Versus NIHSS 0-2. J Stroke Cerebrovasc Dis 2023;9;32(5):107070. https://doi.org/10.1016/j.jstrokecerebrovasdis.2023.107070
- 44. Li X, Wang Y, Xu J. Development of a machine learning-based risk prediction model for cerebral infarction and comparison with nomogram model. J Affect Disord 2022:1:314:341-8. https://doi.org/10.1016/j.jad.2022.07.045
- 45. Kim KS, Oh AR, Park J, Ryu JA. Association between fibringen-toalbumin ratio and prognosis in patients admitted to an intensive care unit. J Clin Med 2023;12(4):1407 https://doi.org/10.3390/jcm12041407
- 46. Chen X, Liu Z, Miao J, et al. High stress hyperglycemia ratio predicts poor outcome after mechanical thrombectomy for ischemic stroke. J Stroke Cerebrovasc Dis 2019;28(6):1668-73. https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.02.022
- 47. Wang L, Zhou Z, Tian X, et al. ACTUAL investigators. Impact of relative blood glucose changes on mortality risk of patient with acute ischemic stroke and treated with mechanical thrombectomy. J Stroke Cerebrovasc Dis 2019;28(1):213-9. https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.09.036
- 48. Rabinstein AA, Albers GW, Brinjikji W, Koch S. Factors that may contribute to poor outcome despite good reperfusion after acute endovascular stroke therapy. Int J Stroke 2019;14:23-31. https://doi.org/10.1177/1747493018799979
- 49. Ozdemir O, Giray S, Arlier Z, et al. Predictors of a good outcome after endovascular stroke treatment with stent retrievers. The Scientific World Journal 2015;1-9. https://doi.org/10.1155/2015/403726
- 50. Hill MD, Demchuk AM, Goyal M, et al. Alberta stroke program early computed tomography score to select patients for endovascu-

- lar treatment interventional management of stroke (IMS)-III trial. Stroke 2014:45(2):444-9.
- https://doi.org/10.1161/STROKEAHA.113.003580
- 51. Singer OC. Haring H-P. Trenkler J. et al. Age dependency of successful recanalization in anterior circulation stroke: the END-STROKE study, Cerebrovascular Diseases 2013;36(5-6):437-45. https://doi.org/10.1159/000356213
- 52. Natarajan SK, Dandona P, Karmon Y, et al. Prediction of adverse outcomes by blood glucose level after endovascular therapy for acute ischemic stroke, Journal of Neurosurgery 2011;114(6):1785-99. https://doi.org/10.3171/2011.1.JNS10884
- Parsons MW, Barber PA, Desmond PM, Baird TA, Darby DG, Byrnes G, et al. Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study. Ann Neurol 2002;52:20-8. https://doi.org/10.1002/ana.10241
- 54. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke 2001;32:2426-32. https://doi.org/10.1161/hs1001.096194
- 55. Pan Y, Jing J, Chen W, Wang Y, He Y. Association between impaired renal function and stroke outcome in patients with versus without atrial fibrillation. Eur J Neurol 2018;25:1041-8. https://doi.org/10.1111/ene.13617
- 56. Liu H, Zheng H, Wu P, Liu CF, Wang D, Li H, et al. Estimated glomerular filtration rate, anemia and outcomes in patients with ischemic stroke. Ann Transl Med 2020;8:2. https://doi.org/10.21037/atm.2019.11.148
- Lima HN, Cabral NL, Goncalves AR, Hauser A, Pecoits-Filho R. Association between albuminuria, glomerular filtration rate and mortality or recurrence in stroke patients. Nephron Clin Pract 2011;117:c246-c252.
- https://doi.org/10.1159/000320342 58. Ovbiagele B, Sanossian N, Liebeskind DS, Kim D, Ali LK, Pineda S, et al. Indices of kidney dysfunction and discharge outcomes in hospitalized stroke patients without known renal disease. Cerebrovasc Dis 2009;28:582-8. https://doi.org/10.1159/000247602