ORIGINAL ARTICLE
https://doi.org/10.1590/1806-9282.20210198

Fibrinogen-to-albumin ratio may be a predictor for ascending aortic aneurysm

Mevlüt Serdar Kuyumcu[1]*, Oğuz Aydın[1]

SUMMARY

OBJECTIVE: The predictive value of the fibrinogen-to-albumin ratio has been evidenced in coronary artery disease. Available data demonstrated that inflammation and oxidative stress are the relevant mechanisms of ascending aortic aneurysm formation and dilatation. The fibrinogen-to-albumin ratio reflects oxidative stress and inflammation. This study investigated the correlation between fibrinogen-to-albumin ratio and ascending aortic aneurysm.

METHODS: A total of 250 consecutive patients with ascending aortic aneurysm and 250 consecutive patients with normal ascending aortic diameter were included in the study using comprehensive transthoracic echocardiography. All data and fibrinogen-to-albumin ratio were compared between two groups.

RESULTS: The fibrinogen-to-albumin ratio levels were significantly higher in ascending aortic aneurysm group compared with normal ascending aortic diameter group ($p<0.001$). Also, there was significantly positive correlation between the diameter of the ascending aorta and the fibrinogen-to-albumin ratio ($p<0.001$).

CONCLUSION: Fibrinogen-to-albumin ratio is associated with ascending aortic aneurysm and may serve as blood marker for identifying high-risk patients.

KEYWORDS: Fibrinogen. Albumin. Ascending aortic aneurysm. Inflammation.

INTRODUCTION

The normal diameter of the ascending aorta depends on the age, sex, and body size of the patient. Aneurysm is a weakening or expansion of the aorta by more than 50% of predicted diameter[1,2]. The most frequent cause of ascending aortic aneurysm (AAA) is cystic medial degeneration, in which the flexible fibers present in the wall of the aorta deteriorate and thin out the wall of the aorta and cause it to dilate and form an aneurysm. This process usually occurs in later decades, at about the age of 60 or 70 years. Smoking and hypertension are also associated with aneurysm development[3]. Inflammatory diseases of the aorta can be classified as a spectrum of diseases with different clinical and histopathological definitions. The most common of these diseases is atherosclerosis, a disease that primarily influences the aortic intima[4,5].

Fibrinogen is a human serum glycoprotein consisting of three pairs of non-superposable polypeptide series[6]. It is the major plasma protein clotting factor. It is also a standard positive acute-phase reactant protein and an independent predictor of coronary artery disease[7]. It has been reported that the fibrinogen-to-albumin ratio (FAR) may be associated with acute coronary syndrome[8], end-stage renal disease[9], hypertension[10], and recurrent stroke[11].

According to the reviews found in literature, the pathogenesis of degenerative AAA could be caused by fibrinogen. Based on this information, the aim of this study was to determine whether the diameter of the ascending aorta or AAA is associated with FAR.

[1]Süleyman Demirel University, Faculty of Medicine, Department of Cardiology – Isparta, Turkey.
*Corresponding author: kuyumcuserdar@hotmail.com
Conflicts of interest: the authors declare there are no conflicts of interest. Funding: none.
Received on April 16, 2021. Accepted on April 21, 2021.

METHODS

For the purpose of this study, the newly diagnosed AAA patients were examined in a series from June 2014 to June 2018. Out of 421 patients in total, those who had acute and chronic hepatitis (n=6), Marfan syndrome (n=3), cardiomyopathies (n=16), arrhythmias (n=12), renal dysfunction (creatinine >1.5 mg/dL; n=21), severe aortic regurgitation (n=10), active infectious disease (n=1), malignancy (n=24), chronic obstructive pulmonary disease (n=41), chronic inflammatory disease (n=3), and dilation solely in the aortic root (n=34) were excluded from our study. So, the remaining AAA patients (n=250) were included. In this study, the control group comprised an equal number of freshly diagnosed high blood pressure patients with normal aortic sizes to the group of freshly diagnosed AAA patients with hypertension, after age and sex matching. This study was approved by the Ethics Committee of the University.

A total of 500 patients were included in this study. Throughout the study, all patients underwent full transthoracic echocardiographic investigation, and dimensions of the aorta were recorded for each patient. AAA was diagnosed when the diameter of the singular abdominal aorta was ≥40 mm. Before carrying out the physical examination, the history of each patient was thoroughly evaluated, and the medical decision utilized 12-channel ECG results. Based on the blood pressure levels, corporally calculated by a mercury sphygmomanometer favorable with the guidelines, when the average value of three records (in two or four visits) for a systolic and a diastolic blood pressure was not less than 140 and 90 mmHg, respectively, this calculated value was clinically defined as hypertension. A glucose level of 126 mg/dL or higher, despite continuing antidiabetic treatment or following a diabetic diet, was evaluated as diabetes mellitus, and as diabetic predisposition when the glucose level reached 100 mg/dL. The classification of active smokers was achieved during diagnosis, independent of the counts of cigarettes smoked. Hyperlipidemia was defined in patients whose total cholesterol (TC) and triglyceride (TG) values were higher than 200 and 150 mg/dL, respectively. The body mass index formula used was [weight (kg)/height (m^2)].

For the main analyses, blood samples were obtained after 12 h of fasting to calculate the plasma glucose, high-density lipoprotein (HDL)-cholesterol, TGs, TC, and low-density lipoprotein cholesterol in all patients. A Horiba hematology analyzer was utilized for complete blood count analysis for the samples in ethylenediaminetetra acetic acid anticoagulated tubes. An analysis was conducted to designate monocyte counts to calculate the monocyte/HDL ratio for each patient. The hospital noted 1–8% as the reference measure for minimum heart rate. The formula of the Chronic Kidney Disease Epidemiology Collaboration was used to estimate the glomerular filtration rate. The nephelometric method was used to determine the high-sensitivity C-reactive protein (hsCRP) levels recognized as baseline, using a Horiba analyzer.

For all the patients, the complete transthoracic assessment was directed based on the aortic size measured through an ACUSON SC2000 PRIME Ultrasound System with a 2.5–3.5 MHz transducer. After collected from the electronic patient registry system, the echocardiography sheets showed at least three sequential beats, and all the view analyses were evaluated by a specialized cardiologist. The highest intra-observer variability coefficient was 5%. Computed tomography was requested for patients scheduled for surgery.

To define left ventricular ejection fraction, the modified Simpson method was performed on an apical four-chambered echocardiogram.

The structural investigation of the aortic valve was carried out on both the parasternal long-axis and short-axis images. The inner diameter of the aortic wall was evaluated. The aortic size was calculated from both the sinotubular junction and the sinus of Valsalva level. The American Society of Echocardiography recommended to measure the size of the proximal ascending aorta using M-mode echocardiography on the parasternal long-axis image in which the largest aortic size can be examined via a leading technique in a vertical plane to the parasternal long axis of the aorta. AAA was determined as an ascending aortic size of higher than 40 mm.

Statistical analysis

The results were statistically analyzed using the SPSS Statistics Version 22.0 Software Package (SPSS Inc., Chicago, USA). The number of patients in each group was adjusted to 250. We calculated the minimum number of individuals who should be sampled with 90% power and 0.05 Type I error as at least 46 (R 3.0.1. open source program). The primary effect variable was determined as the FAR. The 0.1 change FAR was accepted as clinically relevant. Standard deviation of the primary effect variable was calculated as ±0.21. The Kolmogorov–Smirnov test was used to determine the statistical distribution patterns. Mean±standard deviation or percentages were used as the descriptive statistics. Intergroup comparison was accomplished using Mann-Whitney U test for the nonparametric data and Student's *t*-test for the normally distributed or parametric data. The χ^2 test was used for testing the relationships between the categorical variables. The Pearson's or Spearman's correlation test was used to evaluate the linear relationship between two continuous variables when suitable. Stepwise multivariate linear regression analysis and univariate linear regression analysis were used to determine the relationships between potential risk factors and AAA size. The precondition for the multivariate linear regression model was $p<0.10$. The significance level was determined as $p<0.05$ for the statistical analyses.

RESULTS

The demographic, echocardiographic, and drug use characteristics of the patients are shown in Table 1. There was no significant difference between the groups, except for hypertension (p=0.015). The echocardiographic features of the patients are shown in Table 2. AAA significantly enlarged the diameters of vena contracta of aortic regurgitation, the sinus of Valsalva, aortic annulus diameter, sinotubular junction, arcus aorta, and ascending aorta (for all, p<0.001).

The laboratory parameters of the groups are shown in Table 3. The AAA patients had significantly higher levels of hsCRP (p<0.001), uric acid (p=0.027), and fibrinogen (p=0.004). The albumin levels were lower (p=0.041) and the FAR was significantly higher in the patient group.

Table 1. Clinical and demographic characteristics of the study population.

	Control group (n=250)	Case group (n=250)	p-value
LVEF (%)	63.1±2.2	61.0±2.2	0.523
ARVC (mm)	0.8±1.0	2.4±1.0	<0.001
Aortic annulus diameter (mm)	2.19±0.21	2.30±0.37	<0.001
Sinus Valsalva diameter (mm)	3.47±0.71	4.07±0.78	<0.001
Ascending aorta diameter (mm)	3.27±0.24	4.60±1.47	<0.001
Bicuspid aortic valve, n (%)	45 (18.0)	8 (3.2)	<0.001

Data are given as mean±SD, n or median (interquartile range). ARVC: vena contracta width of aortic regurgitation; LVEF: left ventricular ejection fraction.

Table 2. Echocardiographic characteristics of the study population.

	Control group (n=250)	Case group (n=250)	p-value
LVEF (%)	63.1±2.2	61.0±2.2	0.523
ARVC (mm)	0.8±1.0	2.4±1.0	<0.001
Aortic annulus diameter (mm)	2.19±0.21	2.30±0.37	<0.001
Sinus Valsalva diameter (mm)	3.47±0.71	4.07±0.78	<0.001
Ascending aorta diameter (mm)	3.27±0.24	4.60±1.47	<0.001
Bicuspid aortic valve, n (%)	45 (18.0)	8 (3.2)	<0.001

Data are given as mean±SD, n or median (interquartile range). LVEF: left ventricular ejection fraction; ARVC: vena contracta width of aortic regurgitation.

Table 3. Blood parameters of the study population.

	Control group (n=250)	Case group (n=250)	p-value
Glucose, mg/dL	113.9±42.3	109.3±37.1	0.481
Creatinine, mg/dL	1.07±0.25	1.07±0.32	0.749
Uric Acid, mg/dl	5.51±2.37	6.71±2.67	0.027
Hemoglobin, g/dL	13.8±1.4	14.0±1.7	0.410
WBC, $10^3/mm^3$	7.8±2.4	8.1±2.4	0.343
Hs-CRP, mg/L	4.5±2.5	8.4±3.7	<0.001
Total cholesterol, mg/dL	188.9±42.8	181.2±45.3	0.056
LDL-C, mg/dL	118.8±33.8	112.7±45.3	0.291
HDL-C, mg/dL	47.3±10.7	47.7±12.7	0.847
Albumin (g/dL)	3.83±0.09	3.68±0.14	0.041
Fibrinogen (µg/ml)	364±36	467±73	0.004
Fibrinogen-to-albumin ratio	95±10	127±24	<0.001

Data are given as mean±SD, n or median (interquartile range). WBC: white blood cell; Hs-CRP: high-sensitivity C-reactive protein; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; MHR: monocyte – high-density lipoprotein ratio.

The predictors (Tables 1 and 3) of AAA therapy were determined through univariate and multiple linear regression analyses, and the results are shown in Table 4. In the univariate regression analysis, higher hypertension rate (OR 1.518; 95%CI 1.351–1.706; p=0.014), higher hsCRP levels (OR 1.041; 95%CI 1.022–1.061; p<0.001), lower albumin levels (OR 1.051; 95%CI 1.008–1.087; p=0.015), higher fibrinogen levels (OR 1.048; 95%CI 1.030–1.073; p=0.010), and higher FAR (OR 1.201; 95%CI 1.158–1.246; p<0.001) were related to AAA. The multiple linear regression analysis demonstrated that higher hsCRP levels (OR 1.032; 95%CI 1.013–1.1052; p=0.002) and higher FAR (OR 1.224; 95%CI 1.165–1.281; p<0.001) were independent predictors of AAA.

FAR was significantly and positively correlated with the diameter of the ascending aorta (p<0.001, r 0.928; Figure 1).

DISCUSSION

This study determined that increased FAR was associated with the maximum diameter of the ascending aorta. Aortic aneurysm is considered as a separate degenerative process involving all layers of the vessel wall. A wide variety of inflammatory and infective disorders may lead to AAA. *Mycobacterium tuberculosis* is associated with AAA.

Fibrinogen acts a part in blood clotting, fibrinolysis, and inflammatory response[12]. Kannel et al.[13] and Stone et al.[14] identified that fibrinogen is a risk factor for cardiovascular disease. Wilhelmsen et al.[15] reported that fibrinogen is a risk factor for the development of stroke and myocardial infarction. Increased fibrinogen levels are associated with early signs of coronary artery disease in patients[16]. Zhao et al.[17] stated that fibrinogen is associated with coronary collateral circulation in stable coronary artery disease patients.

Serum albumin has been proven to have antioxidant activity and anti-inflammatory effects[2,18,19]. Low serum albumin levels are associated with ischemic heart disease, stroke, and venous thromboembolism[20]. A higher FAR has been found useful in predicting the risk of atrial fibrillation[21]. Özdemir et al.[10] reported that the FAR is associated with hypertensive patients who have inflammation in the pathogenesis of the disease. Biomarkers associated with inflammation have been identified in patients with AAA and dissection[22]. Inflammatory markers, such as fibrinogen, albumin, and CRP, have been used to predict cardiovascular risk[23].

Microvascular dysfunction and inflammation are associated with both fibrinogen elevation and AAA. In the literature, we did not find any study investigating the relationship between the FAR and AAA. Both AAA and FAR are associated with inflammation.

In our study, we determined that FAR was significantly different between the groups, and higher FAR was an independent risk factor for AAA progression. Also in the present study, the FAR was a highly sensitive and specific indicator for predicting the clinical class and disease severity of AAA. AAA is a simple and easily available parameter, which does not necessitate an additional expense. This costless and useful parameter may provide the clinicians to predict patients with AAA, which may cause mortality.

Our study had some limitations. This study is a retrospective cohort study with a comparatively small sample size. We don't

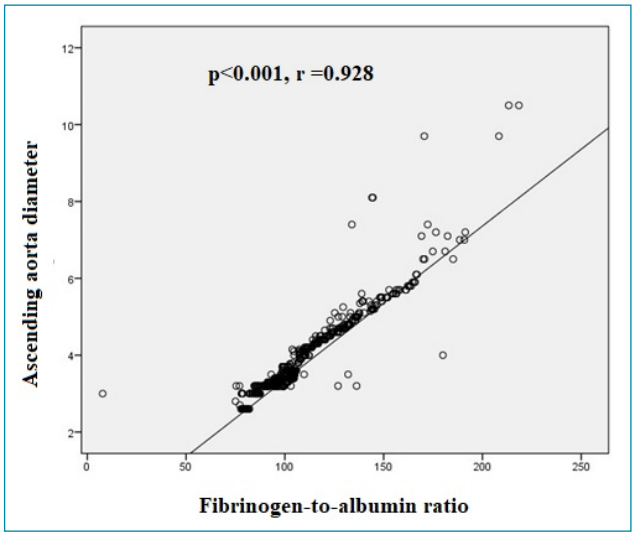

Figure 1. The correlation between fibrinogen-to-albumin ratio and ascending aorta diameter.

Table 4. Multivariate linear regression analysis showing the predictors for the ascending aortic dilatation.

	Univariable Beta (95%CI)	p-value	Multivariable Beta (95%CI)	p-value
Hypertension	1.518 (1.351–1.706)	0.014	1.477 (0.998–2.187)	0.057
Uric Acid	1.045 (0.996–1.099)	0.086		
Hs-CRP	1.041 (1.022–1.061)	<0.001	1.032 (1.013–1.052)	0.002
Albumin	1.051 (1.008–1.087)	0.015	1.066 (1.020–1.123)	0.076
Fibrinogen	1.048 (1.030–1.073)	0.010	1.051 (1.033–1.074)	0.055
Fibrinogen-to-albumin ratio	1.201 (1.158–1.246)	<0.001	1.224 (1.165–1.281)	0.001

Hs-CRP: high-sensitivity C-reactive protein.

have the follow-up major adverse cardiac events data. So, our results should be confirmed by future multicenter prospective longitudinal studies with larger sample size. Then, we gathered only the baseline characteristics of the patients. Therefore, the connection between the dynamic variance in the FAR and outcomes could not be examined. Finally, this study is not a randomized controlled study. Large-scale randomized controlled studies are still needed to further evaluate the predictive value of FAR on the severity of AAA.

AUTHORS' CONTRIBUTIONS

OA: Data curation, Investigation, Writing – original draft. **MSK:** was involved in Methodology, Supervision, Writing – original draft.

REFERENCES

1. Onat A, Hergenç G, Can G. Major influence of dysfunctions of protective serum proteins on cardiometabolic risk among Turks and gender difference. Turk Kardiyol Dern Ars. 2009;37(6):425-34. PMID: 20019460
2. Ayhan H, Bozkurt E. Approach to aortic aortic valve diseases in the elderly. Turk Kardiyol Dern Ars. 2017;45(Suppl 5):47-51. https://doi.org/10.5543/tkda.2017.31526
3. Günay Ş, Güllülü NS. Approach to aortic aneurysms in the elderly. Turk Kardiyol Dern Ars. 2017;45(Suppl 5):93-5. https://doi.org/10.5543/tkda.2017.57034
4. Adaletli I, Selçuk D, Davutoğlu V. Abdominal aortic aneurysm associated with coronary artery aneurysm. Anadolu Kardiyol Derg. 2005;5(3):258. PMID: 16140671
5. Gürer O, Kırbaş A, Bilal MS. Valve-sparing operation for ascending aorta aneurysm. Anadolu Kardiyol Derg. 2011;11(5):456-8. https://doi.org/10.5152/akd.2011.114
6. Alyan O, Kaçmaz F, Ozdemir O, Karahan Z, Taşkesen T, Iyem H, et al. High levels of high-sensitivity C-reactive protein and impaired autonomic activity in smokers. Turk Kardiyol Dern Ars. 2008;36(6):368-75. PMID: 19155639
7. Lowe GD, Rumley A, Mackie IJ. Plasma fibrinogen. Ann Clin Biochem. 2004;41(Pt 6):430-40. https://doi.org/10.1258/0004563042466884
8. He D, Jiao Y, Yu T, Song J, Wen Z, Wu J, et al. Prognostic value of fibrinogen-to-albumin ratio in predicting 1-year clinical progression in patients with non-ST elevation acute coronary syndrome undergoing percutaneous coronary intervention. Exp Ther Med. 2019;18(4):2972-8. https://doi.org/10.3892/etm.2019.7890
9. Yaowei Z, Zhaohua Z, Jingxuan Z, Xiaoyu W, Hongying L, Xiaoqun N, et al. Fibrinogen/Albumin Ratio: A More Powerful Prognostic Index for Patients with End-Stage Renal Disease. Eur J Clin Invest. 2020:e13266. https://doi.org/10.1111/eci.13266
10. Özdemir M, Yurtdaş M, Asoğlu R, Yildirim T, Aladağ N, Asoğlu E. Fibrinogen to albumin ratio as a powerful predictor of the exaggerated morning blood pressure surge in newly diagnosed treatment-naive hypertensive patients. Clin Exp Hypertens. 2020;42(8):692-9. https://doi.org/10.1080/10641963.2020.1779282
11. Beamer N, Coull BM, Sexton G, Garmo P, Knox R, Seaman G. Fibrinogen and the albumin-globulin ratio in recurrent stroke. Stroke. 1993;24(8):1133-9. https://doi.org/10.1161/01.str.24.8.1133
12. Bozdemir V, Kirimli O, Akdeniz B, Ulgenalp A, Aslan A, Kala V, et al. The association of beta-fibrinogen 455 G/A gene polymorphism with left atrial thrombus and severe spontaneous echo contrast in atrial fibrillation. Anadolu Kardiyol Derg. 2010;10(3):209-15. https://doi.org/10.5152/akd.2010.059
13. Kannel WB, Wolf PA, Castelli WP, D'Agostino RB. Fibrinogen and risk of cardiovascular disease: the Framingham Study. Jama. 1987;258(9):1183-6. https://doi.org/10.1001/jama.1987.03400090067035
14. Stone MC, Thorp JM. Plasma fibrinogen--a major coronary risk factor. J R Coll Gen Pract. 1985;35(281):565-9. PMID: 4093900
15. Wilhelmsen L, Svärdsudd K, Korsan-Bengtsen K, Larsson B, Welin L, Tibblin G. Fibrinogen as a risk factor for stroke and myocardial infarction. N Engl J Med. 1984;311(8):501-5. https://doi.org/10.1056/NEJM198408233110804
16. Pilgeram LO. Relation of plasma fibrinogen concentration changes to human arteriosclerosis. J Appl Physiol. 1961;16:660-4. https://doi.org/10.1152/jappl.1961.16.4.660
17. Zhao Y, Wang S, Yang J, Lin Z, Chen Q. Association of fibrinogen/albumin ratio and coronary collateral circulation in stable coronary artery disease patients. Biomark Med. 2020;14(16):1513-20. https://doi.org/10.2217/bmm-2020-0333
18. Türedi S, Karahan SC, Menteşe A, Gündüz A, Topbaş M, Koşucu P, et al. Investigation of relationship between the D-dimer and ischemia-modified albumin levels with the radiological imaging-based pulmonary embolism severity score in acute pulmonary embolism. Anadolu Kardiyol Derg. 2010;10(4):346-52. https://doi.org/10.5152/akd.2010.094
19. Ede H, Yaylak B, Akkaya S, Karaçavuş S, Göçmen AY, Erbay AR. Can ischemia-modified albumin help in differentiating myocardial perfusion scintigraphy results? Turk Kardiyol Dern Ars. 2016;44(5):380-8. https://doi.org/10.5543/tkda.2016.99148
20. Arques S. Human serum albumin in cardiovascular diseases. Eur J Intern Med. 2018;52:8-12. https://doi.org/10.1016/j.ejim.2018.04.014
21. Mukamal KJ, Tolstrup JS, Friberg J, Grønbaek M, Jensen G. Fibrinogen and albumin levels and risk of atrial fibrillation in men and women (the Copenhagen City Heart Study). Am J Cardiol. 2006;98(1):75-81. https://doi.org/10.1016/j.amjcard.2006.01.067
22. He R, Guo DC, Estrera AL, Safi HJ, Huynh TT, Yin Z, et al. Characterization of the inflammatory and apoptotic cells in the aortas of patients with ascending thoracic aortic aneurysms and dissections. J Thorac Cardiovasc Surg. 2006;131(3):671-8. https://doi.org/10.1016/j.jtcvs.2005.09.018
23. Lowe GDO. Circulating inflammatory markers and risks of cardiovascular and non-cardiovascular disease. J Thromb Haemost. 2005;3(8):1618-27. https://doi.org/10.1111/j.1538-7836.2005.01416.x