

# Detection of Negative Acute Phase Reactant Fetuin-A Level In Patients With Pulmonary Embolism

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## ABSTRACT

Pulmonary Thromboembolism (PTE) is a clinical condition with a high mortality rate and various difficulties in diagnosis. The fact that scintigraphy, which may be necessary for diagnosis, and angiography, which is the gold standard for diagnosis, can only be performed in certain centers causes diagnostic efforts to be inadequate in some cases. New markers are needed for early diagnosis and prognostic process in this disease. The aim of this study is to determine the diagnostic value of plasma Fetuin-A test in patients with complaints, examinations and nonspecific laboratory findings suggesting PTE and to investigate its usability as a criterion in PTE disease diagnosis.

This study was designed as a prospective, observational case-control study comprising 31 PTE patients and 30 controls.

It was determined that there was no significant difference between the patient and control groups in terms of age and gender ( $p=0.886$ ,  $p=0.898$ ). There were statistically significant results for white blood cell, albumin, sedimentation rate, C-reactive protein and Fetuin-A values among the groups in our study ( $p<0.05$ ). It was observed that the difference in Fetuin-A levels in patients who exited due to PTE was not statistically significant ( $p=0.698$ ).

Fetuin-A levels were found to be low in patients with acute pulmonary embolism. This finding is consistent with the results of other studies defining Fetuin-A as a negative acute phase reactant. No significant correlation was found between Fetuin-A levels and mortality in patients with pulmonary embolism.

**Keywords:** Pulmonary Embolism, Fetuin-A, Deep Vein Thrombosis

## Introduction

Pulmonary thromboembolism (PTE) is a clinical picture with a high mortality rate and can be difficult to diagnose. PTE is characterised by the occlusion of the pulmonary artery and/or its branches by thrombus, which is usually carried by systemic veins, and sometimes by non-thrombus materials (e.g. air, fat, tumour cells, amniotic fluid, septic material) (1,2).

Obstruction of the pulmonary vascular bed is frequently the result of fragments detached from thrombi occurring in the deep leg veins (in over 90% of cases). Other causative factors, aside from thrombus, have been observed on rare occasions (2,3).

Fetuin-A, also known as alpha-2-Heremans-Schmid (HS)-glycoprotein (Ahsg), is a 64kDa glycoprotein that is secreted by the liver and adipose tissue. It functions as a cysteine protease

inhibitor. It contributes significantly to the migration of macrophages into adipose tissue, resulting in increased pro-inflammatory cytokine expression (for example, IL-6 and TNF- $\alpha$ ) whilst concurrently decreasing adiponectin expression (4,5).

It has been established that Ahsg participates in a multitude of biological functions (see reference list). These functions include the regulation of calcification, tumour growth, endothelial cell function, calcium metabolism, senescence, protein metabolism, insulin signalling, and angiogenesis. In addition, Ahsg has been demonstrated to stimulate the production of inflammatory cytokines in adipocytes and macrophages, thus serving as an indicator of inflammation. However, Ahsg can also function as an anti-inflammatory marker in various diseases, including endotoxemia, sepsis, pancreatitis, chronic kidney disease, and rheumatoid arthritis (6).

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Received: 11.05.2025, Accepted: 01.04.2026

A plethora of studies have demonstrated a correlation between low levels of Fetuin-A and elevated calcification scores, increased arterial stiffness, mortality and the incidence of cardiovascular events (7).

PTE is a condition characterised by the disruption of haemostatic balance, with a high morbidity and mortality rate. A rapid diagnosis is also imperative in reducing mortality rates to 2-8% in treated cases (8,9).

Consequently, there is a necessity for novel markers to facilitate the process of early diagnosis and prognosis in PTE. The objective of this study was twofold: firstly, to ascertain the diagnostic value of the plasma Fetuin-A test in patients with complaints, examination and nonspecific laboratory findings suggestive of PTE; and secondly, to investigate its usefulness as a criterion for the diagnosis of PTE.

## Materials and Methods

This study was designed and conducted as a prospective, observational case-control study. The study included 31 consecutive patients who presented to the emergency department with a suspected diagnosis of pulmonary embolism within a specific time period and whose diagnosis of PTE was confirmed using thoracic computed tomography-angiography (CT-angiography). The control group consisted of 30 healthy volunteers with similar characteristics to the study group in terms of age and gender distribution. For all patients included in the study, a comprehensive assessment was performed, including pulse rate, respiratory rate, systolic blood pressure, ECG findings, cardiac enzymes, D-dimer, blood gases, routine biochemical parameters, and Fetuin-A levels, regardless of the specific underlying causes of PTE.

The primary inclusion criterion in our study was that patients had presented to the emergency department and had been diagnosed with PTE using objective methods. Patients were included in the study regardless of etiological status, age, or gender. To standardize additional factors that could affect Fetuin-A levels, individuals with a history of hematological diseases, active infections, chronic inflammatory conditions, recent myocardial infarction, cerebrovascular disease, decompensated heart failure, diabetes mellitus, and chronic kidney disease were excluded from the study.

Venous blood samples were collected from all participants included in the study at the time of application. Five milliliters of venous blood was collected from individuals in the patient and control groups into yellow-capped gel-filled biochemistry tubes. These blood samples were centrifuged at 4000 rpm for 5 minutes within a maximum of 8 hours, and the resulting serum was collected in Eppendorf tubes and stored at -80°C to determine Fetuin-A levels. Samples stored in accordance with the cold chain were thawed appropriately before the study and analyzed without delay.

Fetuin-A measurements were performed at the Biochemistry Laboratories of Cumhuriyet University Faculty of Medicine Research Hospital. Serum Fetuin-A levels were measured using the Sandwich Enzyme Linked Immunosorbent Assay (ELISA) method. A commercial Fetuin-A kit from Fine Test, containing 96 samples, was used for the measurements. The sensitivity of the measurement method was 0.469 ng/ml; the specificity was stated by the manufacturer as being designed so that the kit would not cross-react with similar non-target molecules, meaning that the measurement was specific to Fetuin-A.

**Statistical Methods:** The findings obtained in the study were evaluated using the SPSS 22.0 (Statistical Package for the Social Sciences, SPSS Inc, Chicago, USA) program. The distribution of variables was assessed for normality using the Kolmogorov-Smirnov test. Descriptive statistics were presented as Mean  $\pm$  Standard Deviation (SD) for normally distributed data, and as Median (Interquartile Range - IQR) for non-normally distributed data or small sample groups, such as the non-survivor group in Table 3.

For the comparison of independent groups, the Student's t-test was employed for normally distributed variables after confirming the homogeneity of variances. In instances where the data were not normally distributed or the sample size was insufficient for parametric testing, the Mann-Whitney U test was utilized. For the comparison of multiple parameters in Table 2, the potential for Type I errors was addressed by considering multiple comparison corrections (e.g., Bonferroni correction) in the interpretation of the results.

Categorical variables were analyzed using the Chi-square test. To maintain consistency and precision, all p-values are reported with three decimal places. A p-value less than 0.050 was considered to be statistically significant.

## Results

A statistical analysis was conducted, which revealed no significant differences between the patient group and the control group with regard to age and gender ( $p=0.886$ ,  $p=0.898$ ) (Table 1).

A subsequent analysis of the data yielded statistically significant results for white blood cell, albumin, sedimentation rate, C-reactive protein, d-dimer and Fetuin-A values in both groups ( $p<0.05$ ). In addition, a lower median value of Fetuin-A and Albumin was observed in the patient group when compared to the control group. In contrast, leucocyte, sediment, d-dimer and C-reactive protein values were found to be significantly higher in the patient group. On the other hand, Ca was lower in the patient group and the difference was found to be insignificant ( $p>0.05$ ) (Table 2, Figure 1, Table 3).

In the total cohort of 31 patients, 3 patients died. The variation in Fetuin-A levels among the samples obtained from these patients was not found to be statistically significant (Table 4).

## Discussion

Pulmonary embolism is a clinical picture with a high mortality rate and can be difficult to diagnose. The fact that scintigraphy, which may be necessary for the diagnosis, and angiography, which is the gold standard in diagnosis, can only be performed in certain centres and cannot be applied in all patients, causes diagnostic efforts to be inadequate in some cases. This underscores the necessity for the development of novel markers that can facilitate the early diagnosis and enhance the prognostic process in this disease.

The aim of this study was to evaluate the usefulness of plasma Fetuin-A as a criterion for diagnosing PTE disease with complaints, examination and nonspecific laboratory findings and to determine its prognostic significance.

Fetuin-A is also an effective anti-calcification glycoprotein. In vitro studies have shown that fetuin-A forms complexes with calcium and phosphorus and increases their solubility in a manner similar to apolipoproteins that increase lipid solubility (9).

Fetuin-A binds with serum calcium and phosphate to form small calcific protein particles, which are likely to be absorbed by the reticuloendothelial system and normal kidney (10).

In our study, the mean calcium level of 31 patients was 8.74 mg/dL and the mean calcium level of 30

control subjects was 9.11mg/dL. Although no statistically significant difference was observed ( $p=0.074$ ), a positive correlation was found between calcium and fetuin-A levels (Table 2).

As with albumin, fetuin-A is synthesised in the liver and its synthesis is down-regulated during inflammation. Stenvikel et al. reported a positive correlation between hypoalbuminemia and fetuin-A deficiency in their study (11).

In a study conducted by Lin, Hsin-Hung et al., a significant correlation was demonstrated between serum albumin levels and haemodialysis (HD) patients baseline serum fetuin-A levels, as well as a negative correlation with HD duration. Consequently, the researchers predicted that serum fetuin-A concentrations would be lower in patients with longer HD duration and lower serum albumin levels (12).

The study revealed a statistically significant difference in serum albumin levels between patients suffering from pulmonary embolism (an inflammatory process) and a control group. The mean serum albumin level was determined to be 3.69 g/dl among the patient group and 4.47 g/dl among the control group. This finding indicates a positive correlation between albumin and fetuin-A, thereby supporting the hypothesis that fetuin-A functions as a negative acute phase reactant. Furthermore, an inverse relationship has been observed between CRP levels and fetuin-A. This inverse relationship also exists between fetuin-A and inflammation (13).

Fetuin-A levels have been demonstrated to exhibit an inverse correlation with the concentrations of pro-inflammatory cytokines (IL-1 $\beta$ , IL-6 and TNF- $\alpha$ ) in blood serum or plasma (14).

Ketteler et al. discovered that patients suffering from chronic renal failure undergoing stable haemodialysis exhibited low levels of fetuin-A, which was inversely associated with C-reactive protein levels which is an indicator of inflammation (15).

Increased levels of CRP are indicative of the presence and severity of inflammation. As a cytokine-mediated response to tissue damage, inflammation and infection, the circulating level of C reactive protein can increase 1000-fold and decrease to basal levels within 7-12 days (16).

C-reactive protein is a marker of inflammation that has been shown to be a precursor of ischaemia events and to provide information about the clinical status of patients with coronary artery disease. A body of research has reported a negative correlation between serum CRP and

**Table 1:** Demographic Characteristics of The Case Group vs. Control Group

Characteristics	Case Group (n= 31, %)	Control Group (n= 30, %)	P value (Chi squared test)
Age, year (Mean $\pm$ SD)	68.0 $\pm$ 18.2	68.1 $\pm$ 18.6	0.898*
Gender			
Female	14 (45.2)	13 (43.3)	0.886
Male	17 (54.8)	17 (56.7)	

\*Student t-test

**Table 2:** The Mean Values of Blood Parameters of Patient Group vs Control Group

Variables	Patient Group (N= 31 mean $\pm$ SD)	Control Group (N= 30 mean $\pm$ SD)	P-value*
White blood cell ( $10^3/\mu$ l)	15.4 (1.8)	7.8 (2.3)	0.001
Albumin (g/dL)	3.7 (0.6)	4.5 (0.5)	0.001
Calcium (mg/dl)	8.7 (0.8)	9.1 (0.5)	0.074
Sedimentation Rate (mm/hr)	53.7 (17.3)	11.0 (5.5)	0.001
C-reactive protein (mg/L)	80.2 (50.3)	7.6 (2.5)	0.001
d- dimer (mg/L)	2663.1 (3651,6)	225.1 (167,1)	0.000
Fetuin-A (ng/dL)	196.5 (20.8)	228.1 (35.2)	0.002

\*Student t-test

**Table 3:** Sensitivity and Specificity Values of Fetuin-A and d-dimer Parameters In The Patient Group and The Control Group

	AUC (95% CI)	Cutt off	p	Sensitivity (%)	Specifity (%)
Fetuin-A (ng/dL)	0,728 (0,6-0,855)	221,14	0,002	96,80	50
d-dimer (mg/L)	0,960 (0,911-1)	472,00	0,000	93,50	100

**Table 4:** Fetuin-A levels In Patients With Pulmonary Embolism Were Classified According To Survival and Non-Survival

Variables	Survive (N= 28 mean $\pm$ SD)	Non-Survive (N= 3 medyan Min- Max)	P-value (Mann-Whitney U test)
Fetuin-A (ng/dL)	196 $\pm$ 20.5	218,1 (162,1- 223,3)	p=0,698

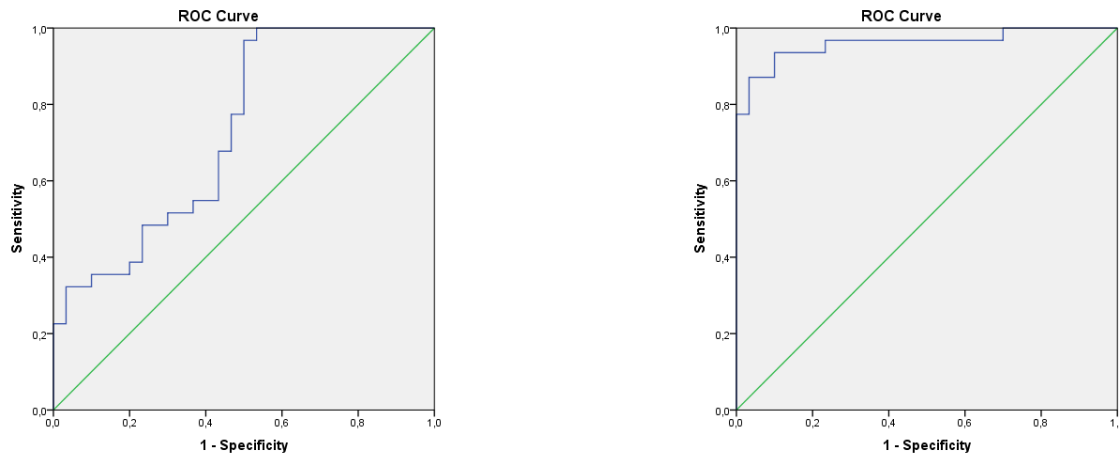
fetuin-A in patients suffering from coronary artery disease (17,18).

Borsky et al. analysed the risk of cardiovascular disease with CRP and Fetuin-A in a study of patients with Psoriasis Vulgaris. The study revealed a significant correlation between elevated CRP levels (3.1 mg/L for the patient group; 309.81 mg/L for the control group;  $P < 0.001$ ) and reduced Fetuin-A levels (266.6  $\mu$ g/ml for the patient group; 309.8  $\mu$ g/ml for the control group;  $P < 0.05$ ) in patients with cardiovascular vascular pathologies (19).

Erythrocyte sedimentation rate (ESR) is one of the tests commonly used to evaluate the acute phase response. It increases 24 hours after the onset of inflammation and recovery may take up

to one month (20). Therefore, a negative correlation is expected between fetuin-A, which is considered to be a negative acute phase reactant, and sedimentation.

In this study, a statistically significant negative correlation was identified between sedimentation, blood leucocyte and CRP levels, and fetuin-A in patients diagnosed with pulmonary embolism. Furthermore, a statistically significant positive correlation was identified between fetuin-A and albumin, as well as serum calcium levels, both within the patient group and across the entire study population. These findings lend further support to the prevailing hypothesis that fetuin-A functions as a negative acute phase reactant. The negative correlation of fetuin-A with positive



**Fig. 1.** ROC Analysis of Fetuin-A and d-Dimer Parameters In Patient And Control Groups

acute phase reactants is consistent with this hypothesis.

In their investigation, Manolakis et al. examined the levels of fetuin-A in patients suffering from inflammatory bowel disease. Their findings indicated a close correlation between the down-regulation of Fetuin-A and the acute phase response, suggesting its potential as a diagnostic and predictive molecule in chronic inflammatory processes associated with both Crohn's disease and ulcerative colitis. The study concluded with the observation that fetuin-A levels were significantly lower in inflammatory bowel disease (21).

*Streptococcus pneumoniae* is able to colonise the upper respiratory tract of humans, with the subsequent potential to cause mucosal infections, including sinusitis, otitis media and pneumonia. Furthermore, it can also lead to invasive pneumococcal diseases (IPD), such as complicated pneumonia (e.g. empyema and necrotising pneumonia), bacteraemia and meningitis (22).

Janapatla et al. confirmed the usefulness of C-reactive protein (CRP) as a biological marker for the severity of pneumococcal pneumonia. The researchers asserted that the qualitative and quantitative analysis of serum fetuin-A in pneumococcal infections can facilitate the identification of complicated pneumonia caused by *S. pneumoniae*. Furthermore, they proposed that serial measurements of fetuin-A have the potential to reflect the response to treatment and recovery from pneumonia in patients with invasive pneumonia. The researchers concluded that fetuin-A should be incorporated into the panel of biomarkers currently utilised for severe invasive pneumonia (23).

Ketteler and colleagues corroborated the finding that reduced serum fetuin-A levels are present in patients with end-stage renal failure (ESRD), and that the diminution of this glycoprotein, which is derived from the liver, is associated with inflammation. The study also established that low levels of fetuin-A can serve as a predictor of both all-cause and cardiovascular mortality in patients with ESRD. The mean fetuin-A level was found to be significantly lower in ESRD patients exhibiting signs of inflammation (24).

Stenvinkel et al. found that high C-reactive protein (CRP), low albumin and low fetuin levels were significantly associated with the presence of carotid plaques. In their study, they demonstrated that low fetuin-A levels are a significant risk factor for inflammation and malnutrition-related mortality in patients with end-stage renal disease (ESRD) receiving renal replacement therapy. The finding that fetuin-A levels are markedly lower in carotid plaques lends further support to the hypothesis that low fetuin-A levels promote accelerated atherosclerosis and vascular calcification. Furthermore, the study revealed that genetic variation in *AHSG* Thr256Ser has a significant impact on serum fetuin-A levels and patient outcomes, particularly in cases exhibiting signs of inflammation (25).

Fetuin-A, a negative acute phase reactant, is hypothesised to decrease in pulmonary embolism as a consequence of inflammation. In the present study, a statistically significant difference ( $p=0.002$ ) was identified between the patient and control groups with regard to fetuin-A levels. The fetuin-A level of the patient group was found to be 196.46 ng/dL, while the fetuin-A level of the control group was found to be 228.10 ng/dL. This finding indicates that the level of fetuin-A

decreased in patients with pulmonary embolism (see Table 2).

In a study conducted by Minas et al., 100 patients with COPD stages 1- 4 were examined. The objective of the study was to investigate the change in Fetuin-A levels during the exacerbation period of COPD and the change between clinical staging and Fetuin-A levels within a 1-year period. A control group consisting of 40 healthy subjects was included in the study. The study revealed that Fetuin-A levels in the patient group were significantly lower than in the control group ( $p < 0.001$ ). Furthermore, Fetuin levels in stage 4 COPD patients were lower than in stage I, II, III groups. Furthermore, it was observed that Fetuin-A levels were diminished during exacerbation periods in comparison to stable periods ( $p < 0.001$ ) (26).

In a further study investigating the relationship between vascular diseases and fetuin-A, Ciftci et al. compared 60 patients with ST elevation MI and 60 patients Non-ST elevation with control groups. There was a significant decrease in fetuin A levels in the patient group. Also a correlation analysis was conducted between high sensitive cardiac troponin-T and monocyte chemotactic protein-1, fetuin-A, serum total antioxidant status, and serum total oxidant status. The analysis revealed that fetuin-A was identified as the closest parameter to hs-cTnT (area under the curve (0.815), sensitivity (73.3%), and specificity (66.7%) (27).

In order to establish a correlation between fetuin-A and the severity of illness, as well as to provide an indication of the probability of survival, Karampela et al. undertook an analysis of the plasma bilirubin/Fetuin-A ratio in a cohort of critically ill patients with sepsis. The study revealed that, upon its conclusion, there was an increase in bilirubin and fetuin-A levels during the initial week of the disease. However, the bilirubin/fetuin-A ratio remained unchanged. Notably, the levels of bilirubin/fetuin-A were found to be significantly higher in patients with septic shock ( $N = 38$ ) and nonsurvivors ( $N = 28$ ) compared to patients with sepsis ( $N = 52$ ) and survivors ( $N = 62$ ), respectively (28).

In the present study, three out of a total of 31 patients deceased. A statistically significant difference was identified between the Fetuin-A levels of the patient group and the control group; however, no significant difference was found between the exitus patients and the control group ( $p=0.698$ ). The Fetuin-A level of one of the deceased patients (200.97 ng/dL) was lower than

the mean Fetuin-A level of the patient group (196.47 ng/dL). The absence of a statistically significant difference in terms of mortality can be attributed to the inability to form a sufficient number of groups due to limitations in both budget and patient numbers. Consequently, it is recommended that future studies encompass a larger patient cohort in order to establish a correlation between Fetuin-A levels and mortality in pulmonary embolism patients.

In this study, the relationship between Fetuin-A, a parameter that has not been studied before, and the inflammatory process in pulmonary embolism patients was evaluated. Blood samples obtained from the patient and control groups were analysed for other inflammatory parameters, especially serum Fetuin-A level. A significant relationship was found between the negative acute phase reactant Fetuin-A and the inflammatory process. Consequently, Fetuin-A levels were found to be low in patients with acute pulmonary embolism. A negative correlation was identified between Fetuin-A and C-reactive protein, as well as between Fetuin-A and the levels of sedimentation rate and blood leucocytes, which increased in cases of inflammation in pulmonary embolism patients. This finding aligns with the conclusions of other studies that have identified Fetuin-A as a negative acute phase reactant. In the present study, a positive correlation was identified between serum calcium and albumin levels and Fetuin-A levels. However, no significant correlation was found between fetuin-A levels and mortality in patients with pulmonary embolism. Consequently, there is a clear need for further research in this field, specifically prospective randomised studies with a larger number of patients.

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