

## Does suPAR Have Diagnostic Importance in Bronchoalveolar Fluid?

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### Abstract

suPAR could contribute to the early diagnosis of lung cancer and tuberculosis.

**Materials and methods:** Bronchoscopy and bronchoalveolar lavage were performed on 66 patients with a pre-diagnosis of lung malignancy and tuberculosis who applied to Harran University Hospital. Simultaneous blood samples were taken. suPAR was studied with the ELISA method. It was compared with 30 healthy individuals as the control group. Informed consent was obtained from the patients for the study.

**Results:** In the patient group, the median plasma suPAR level was 229.59 ng/L and the BAL fluid level was 45.73 ng/L. The median plasma suPAR level of patients with malignancy was 199.40 ng/L, 246.09 ng/L in TB patients and 234.60 ng/L in other diseases. In BAL fluid, the median plasma suPAR level was found to be 56.78 ng/L in patients with lung cancer, 39.24 ng/L in patients with TB, and 44.00 ng/L in other diseases. When the patient and control groups were compared, a significant difference was found in the median plasma suPAR level.

In the study, it was found that plasma suPAR level decreased with age (plasma levels of suPAR for each year was 1.08 ng/L), while it increased with age in the healthy group. In our study, a significant difference was found between the plasma levels of suPAR in the patient and control groups. The mean plasma levels of suPAR ratios of the patients and healthy individuals were statistically significant and the cut-off level was 136.61 ng/L suPAR, BAL fluid level was not statistically significant.

**Conclusion:** In our study, plasma level of suPAR in patients with malignancy may be a nonspecific marker in the pre-diagnosis period, and may also be a useful prognostic marker in predicting negative outcomes in the post-diagnosis period. In our study, plasma level of suPAR above the mean in male patients with primary lung

adenocarcinoma raise the question of whether there is a difference between cancer subtypes and genders.

**Keywords:** Bronchoalveolar fluid; suPAR; Lung cancer; Tuberculosis

### Introduction

Tuberculosis (TB) is the cause of hundreds of thousands of deaths in the world every year and continues to be an important public health problem [1]. For the diagnosis of pulmonary tuberculosis, bacillus should be shown in the sputum smear. The gold standard in diagnosis is the production of bacillus in culture [2]. TB may radiologically resemble and mimic any lesion [3].

Lung cancer is the most common cause of cancer related deaths in men and women, causing more than one million deaths per year [4]. Most of the cases diagnosed with lung cancer are caught at an advanced stage. Studies on this subject have shown that an average of 35 to 50 days is required to reach the diagnosis and start treatment [5].

The radiological manifestations of tuberculosis may be confused with lung cancer. TB is often misdiagnosed with lung cancer and varying clinical presentations, resulting in delayed treatment initiation. This results in unnecessary diagnostic procedures. This situation delays the diagnosis of possible lung cancer and causes the patient to reach treatment late due to the advanced diagnosis. As a result, it causes increased morbidity and mortality. Like consolidations with irregular edges and thick-walled spaces, radiological features suggestive of malignancy, showing high metabolic activity in Positron Emission Tomography/Computed Tomography (PET/CT) imaging, are also typical for tuberculosis cases seen in the thorax [6].

The normal plasma level of suPAR, an immune-activated protein, is below 3 ng/mL in healthy individuals and above 6 ng/mL in critically ill patients. Low levels indicate a good prognosis and support the patient's decision to treat. High levels

indicate the presence, progression and severity of the disease and support greater clinical interest [7].

We aimed to investigate the contribution of suPAR levels in bronchoalveolar lavage fluid and plasma to the diagnosis of TB and Lung cancer in the early period and its usability as a serological marker.

## Materials and Methods

Patients who were admitted to the Harran university faculty of medicine, chest diseases and thoracic surgery outpatient clinics with pathology in their radiological imaging and undergone bronchoscopy were included in our study. Approval for our study was obtained from the ethics committee of Harran university, faculty of medicine. Our study was a prospective study. Bronchoscopy was performed on 66 patients with pulmonary tuberculosis, lung cancer and other diagnoses. Plasma samples were taken simultaneously with bronchoalveolar lavage fluid from these patients. The materials were frozen at  $-80^{\circ}\text{C}$ . suPAR was studied with the ELISA method. The suPAR levels were determined in the collected BAL and plasma. These patients were compared with the suPAR level studied from plasma samples taken from 30 healthy individuals.

## Statistics

Continuous variables were expressed as mean  $\pm$  standard deviation, and categorical data as numbers and percentages.

**Table 1:** Demographic data of the patients.

Age	TB	CA	Others	Control	Mean
Gender M/F	08/3	10/3	28/13	17/13	
Plasma suPAR	246,09	199,4	234,59	108.2	221,38
BAL suPAR	39,24	56,78	44,00	--	45,73
Control plasma suPAR					108,2

In the comparison of plasma suPAR level of the patients between genders,  $p=0.544$ , with  $p>0.05$ . The median plasma suPAR level of concentration in men and women was not significantly different in the patient group. When the same comparison was made between healthy individuals,  $p=0.410$  was not found statistically significant. In this case, we can say that there was no significant difference between the genders in the plasma suPAR level of sick and healthy individuals.

When the BAL suPAR level was compared among the patients in terms of gender,  $p=0.168$ , was not statistically significant. The median BAL suPAR level of men and women were not significantly different in the patient group.

While the median plasma suPAR level of sick individuals was 229.59 ng/L, this rate was found to be 45.73 ng/L in

Comparisons of categorical data were made with the *Chi-square* test (Pearson, Fisher's exact test or linear by linear association, as appropriate). Analyzes were performed with IBM SPSS version 26.0 (IBM Corporation, Armonk, NY, USA). Cases where the type 1 error level was below 5% were considered significant.

## Results

Bronchoalveolar lavage was performed on 66 patients participating in the study. Of these, 46 (69.69%) were male and 20 (30.31%) were female. As the control group, plasma was taken from 30 healthy individuals. Of these, 17 (56.7%) were male and 13 (43.3%) were female. Considering the difference between the plasma levels of suPAR in the patients and healthy individuals. The median plasma suPAR level concentration of the patients was  $229.59 \pm 79.03$  ng/L. In healthy individuals, the mean was  $108.2 \pm 2.14$  ng/L. This rate was found to be statistically significant ( $p<0.05$ ). The median plasma suPAR level of the patient group was 121,381 ng/L higher than the control group. Cut off level was found as 136.61 ng/L. The plasma level of suPAR was found to be statistically significant in sick individuals (**Table 1**).

bronchoalveolar fluid. When the plasma suPAR level of the patients were evaluated among themselves, it was seen that lung cancer, tuberculosis and other diseases were not significant among themselves  $p>0.05$ .

Among the BAL suPAR level of the patients, the p-value for all three diagnoses (cancer, tuberculosis, others) was  $>0.05$ , and the diagnoses did not have a significant effect on the BAL fluid levels. Since all p values were not greater than 0.05, it was observed that the "fluid" dependent variable did not have a normal distribution in all three diseases (cancer, tuberculosis and others), but the BAL suPAR level were found statistically significant level in the diagnoses themselves (**Table 2**).

**Table 2:** Comparison of plasma suPAR levels of the patients according to the groups.

Age	Patients plasma suPAR (ng/L)	Control plasma suPAR (ng/L)
	mean ± SS	mean ± SS
Less 30 years	264,81 ± 64,15	102,04 ± 11,80
31-59 years	243,97 ± 86,78	105,06 ± 10,96
More than 60 years	203,63 ± 65,16	114,76 ± 13,33
Test value/p	3,544/0,034	2,912/0,072
Gender		
Female	240,32 ± 71,53	108,22 ± 12,10
Male	229,07 ± 80,71	110,31± 14,20
Test value/p	0,544/0,588	0,410/0,674

In the patient group, when the age variable increases by 1 year, that is, when the patients' age for 1 year, the levels of the plasma level decreases by 1.08 (ng/L). It was observed that the plasma suPAR level of the patients decreased as their age increased. It was found to be statistically significant as the p-value=0.035<0.05. In the bronchoalveolar fluid, it was observed that the suPAR levels did not increase with age (p-value=0.671>0.05). It was not found statistically significant.

The mean plasma suPAR level of the lung cancer cases was 199.40 ± 77.65 ng/L. This rate was found to be 246 ± 63.76 ng/L in tuberculosis. These rates were not statistically significant when compared to other diseases. The mean suPAR level of patients with lung cancer in the bronchoalveolar fluid was 56.78 ± 21.38 ng/L. This rate was 39.24 ± 24.99 ng/L in cases with tuberculosis. It was not statistically significant when compared to other diseases.

However, when suPAR level in the plasma and bronchoalveolar fluid are examined in terms of diagnoses, the BAL/Plasma suPAR ratio is 0.34, 0.16, 0.21 (lung cancer, tuberculosis and other diseases), respectively, and when the diseases are compared with each other, lung cancer was found to be statistically significant from other lung pathologies (p=0.01).

## Discussion

In our study, in which we investigated the use of suPAR levels in bronchoalveolar lavage and plasma samples as an early and serological marker in the diagnosis of TB and lung cancer, a total of 66 patients and 30 healthy individuals were compared. In our study, there were 13 patients with lung cancer and 11 patients with active TB. In our study, it was found that plasma suPAR level decreased with age (patients' plasma suPAR levels was 1.08 ng/L for each year), while it increased with age in the healthy group. It was found that they were similar in terms of gender and there was no statistically significant difference between the groups for gender and age variables. In our study, a significant difference

was found between the plasma suPAR levels of the patient and control groups. While the median plasma suPAR level was 229 ng/L in the patient, this rate was found to be 108 ng/L in healthy individuals. This rate was statistically significant and the cut-off level was 136.61 ng/L. In BAL fluid median suPAR level was found to be 56.78 ng/L in patients with lung cancer, 39.24 ng/L in patients with TB and 44.00 ng/L in other diseases.

suPAR level in BAL fluid was not statistically significant. Lung cancer is the leading cause of death from cancer. Urokinase Plasminogen Activator (uPA) is present in the cell. It has a soluble form in the cell membrane and circulation. This allows both binding and activation of uPA. It thus leads to the conversion of the plasmin gene to plasmin and the resulting proteolytic activity to be associated with plasmin. With this increase, plasmin can affect the spread of cancer in various ways. Through plasmin, cancer cells are either directly promoted to cell migration or disrupted by the extracellular matrix [8].

In lung cancer, suPAR level increases in plasma as a result of shed surface tumor cells and their metastases [9]. *Mycobacterium tuberculosis* affects the lives of millions of people worldwide, and it is estimated that more than two million people worldwide die from the disease each year. In our study, which is a prospective cohort study, the definitive diagnosis of the patients was a pathological diagnosis of lung cancer and microbiological culture positivity for tuberculosis. Diagnosis of lung cancer (CA) and pulmonary Tuberculosis (TB) requires time. Early diagnosis is difficult. Early diagnosis of both diseases is important in terms of mortality and morbidity, is it possible to contribute to the diagnosis with suPAR? It has been shown in previous studies that suPAR activity, one of the serological markers whose applicability has been investigated in the diagnosis of TB and CA, increases in the fluids, plasma and serum of patients [10]. In our study, the contribution of the results obtained to the differential diagnosis of CA, TB and other (interstitial lung disease, fungal infections, benign radiology) diseases were investigated by comparing the plasma and BAL suPAR levels of CA, TB and other cases with the plasma suPAR

level of healthy subjects. The question of whether it can be a rapid, sensitive and specific method for early diagnosis of patients was examined. Increases plasma suPAR levels have been helpful in evaluating the invasion and metastasis process of lung cancer [8]. suPAR, as a promising biomarker, has been shown to be related to prognosis in patients with lung, breast, ovarian and colon cancer patients with increased plasma levels [11].

In our study, it was observed that suPAR increased levels in the plasma lung cancer cases, but it was not significant in the differential diagnosis from other diseases ( $p>0.005$ ). A comment could not be made because no comparison was made for BAL. Based on the BAL/Plasma suPAR levels in our study, we found it statistically significant compared to other diseases when we used it in lung cancer cases. It can be suggested to us to use the ratio of the BAL and plasma levels of suPAR in the evaluation of cancer risk algorithms. suPAR levels are not only elevated in infections but also in malignancies, infections, or other inflammatory processes such as chronic pleuritis [12].

SUPAR also contributes to the diagnosis of traditional biomarkers (CRP, LDH) [13]. In our study, BAL and plasma suPAR levels were found to be significant between the patient and control groups, but not between diseases. In addition, the ratio of BAL/Plasma suPAR level was significant among the patient groups.

In the studies conducted by Rasmussen et al., it was stated that suPAR increased in the plasma of individuals included in the study with ageing. (0.1 ng/ml per year) (12,13). In our study, we found that the plasma level of suPAR decreased with age ( $p=0.0035$ ), and it did not increase in the bronchoalveolar fluid ( $p=0.671$ ). We reached a finding contrary to Ramusse's study. We have considered a heterogeneous group in the form of lung cancer, TB and other lung diseases (Figure 1).

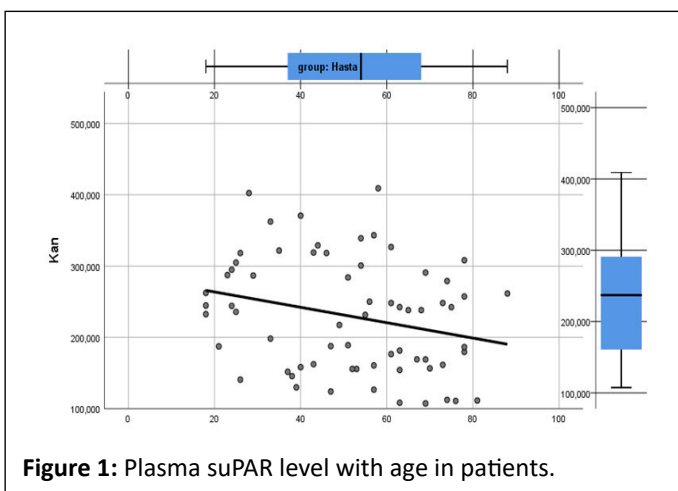


Figure 1: Plasma suPAR level with age in patients.

In our study, no significant difference was found in terms of gender and age in suPAR levels in both plasma and BAL fluid. In our study, plasma suPAR level was high in patients with lung cancer and was not specific. In a previous CE study by Bock et al., it was concluded that high suPAR levels are associated with an increased risk of respiratory and other types of cancer, but not with gastrointestinal cancers (Figure 2) [8,10,14,15].

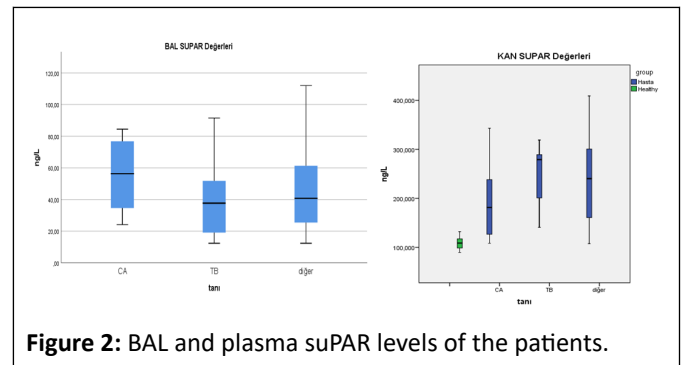


Figure 2: BAL and plasma suPAR levels of the patients.

In our study, the median plasma suPAR level of lung cancer patients was found to be 199.4 ng/dl. When our cancer cases were examined, primary adenocarcinoma cases were five patients and two of them were female patients. The average of their plasma suPAR level was 179.91 ng/dl, which was below the mean value. The median plasma suPAR level of male patients was 301.30 ng/dl, which was higher than the mean value. The average BAL suPAR level of patients diagnosed with adenocarcinoma was 33.53 ng/dl for women and 61.45 ng/dl for men. The BAL suPAR levels of women were found to be lower than the average suPAR levels. This brought to mind the question of whether there was a gender difference in malignancies. Therefore, the difference could not be detected. Otherwise, the majority of gastrointestinal cancers are adenocarcinomas and it raised the question of whether the plasma level was low in the female population.

## Conclusion

In our study, while there was a lower plasma suPAR levels of healthy individuals, it was found to be elevated when compared to patients with malignancy or other diseases. While this may be a nonspecific marker in the pre-diagnosis period, it can also be a useful prognostic marker in predicting negative outcomes in the post-diagnosis period.

In addition, our study revealed the necessity of clarifying the answer to the question of whether there is a difference between cancer subtypes and genders, as plasma suPAR levels are above the average in male patients with primary lung adenocarcinoma.

## Limitations

Although the plasma suPAR levels were high in male patients with adenocarcinoma in our study, the limited number of patients and the heterogeneity of the diseases were the limitations of the study.

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