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The Diagnostic Potential of Blood Soluble Urokinase Plasminogen Activator Receptor Levels in Lung Cancer and Tuberculosis Patients

Hamdiye Turan[1], Atalay Şahin[2], Nihayet Bayraktar[3], Zeynal Yasacı[4], Hamza Erdoğdu[5], Şerif Kurtuluş[6]

1 Department of Chest Diseases, Faculty of Medicine, Harran University, Şanlıurfa, Türkiye

2 Department of Chest Surgery, Faculty of Medicine, Harran University, Şanlıurfa, Türkiye

3 Department of Medical Biochemistry, Faculty of Medicine, Harran University, Şanlıurfa, Türkiye

4 Inonu University, Faculty of Health Sciences, Division of Physiotherapy and Rehabilitation, Malatya, Türkiye

5 Department of Statistics, Faculty of Administration and Economics, Harran University, Şanlıurfa, Türkiye

6 Department of Chest Diseases, Mehmet Akıf Inan Education and Training Hospital, Şanlıurfa, Türkiye

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Abstract

Aim: The study aimed to investigate the potential role of soluble urokinase plasminogen activator receptor (SUPAR) levels in the blood and bronchoalveolar lavage (BAL) fluid for the early diagnosis of lung cancer and tuberculosis (TB).

Methods: Bronchoscopy and BAL were performed on 66 patients with a prediagnosis of lung malignancy or tuberculosis. SUPAR levels were measured using the ELISA method and compared with those from 30 healthy individuals as the control group.

Results: Blood SUPAR, values were 199.40 ng/L in malignancy patients, 246.09 ng/L in TB patients, and 234.60 ng/L in others. In BAL fluid, values were 56.78 ng/L in lung cancer patients, 39.24 ng/L in TB patients, and 44.00ng/L in other diseases. Significant differences were found in blood SUPAR between patients and controls ($p<0.05$). The cut-off value for blood SUPAR was 136.61ng/L.

Conclusion: Elevated blood SUPAR levels in patients with lung cancer may indicate a nonspecific marker during pre-diagnosis and a prognostic marker for predicting negative outcomes post-diagnosis.

Keywords: Bronchoalveolar fluid, SUPAR, lung cancer, tuberculosis.

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Correspondence / Yazışma Adresi: *Zeynal Yasaci, Inonu University, Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Malatya, Türkiye e-mail: zeynalyasaci@gmail.com*

Akciğer Kanseri ve Tüberküloz Hastalarında Kan Çözünür Ürokinaz Plazminojen Aktivatör Reseptörü Düzeylerinin Tanısal Potansiyeli

Öz

Amaç: Bu çalışmada akciğer kanseri ve tüberkülozun (TB) erken tanısında kan ve bronkoalveolar lavaj (BAL) sıvısındaki çözünür ürokinaz plazminojen aktivatör reseptörü (SUPAR) düzeylerinin potansiyel rolü araştırılmıştır.

Yöntemler: Akciğer malignitesi veya tüberküloz ön tanısı olan 66 hastaya bronkoskopi ve BAL uygulandı. SUPAR düzeyleri ELISA yöntemi kullanılarak ölçüldü ve kontrol grubu olarak 30 sağlıklı bireyden elde edilenlerle karşılaştırıldı.

Bulgular: Kan SUPAR değerleri malignite hastalarında 199.40 ng/L, TB hastalarında 246.09 ng/L ve diğerlerinde 234.60 ng/L idi. BAL sıvısında değerler akciğer kanserli hastalarda 56.78 ng/L, TB hastalarında 39.24 ng/L ve diğer hastalıklarda 44.00ng/L idi. Kan SUPAR değerlerinde hasta grup ve kontrol grubu arasında anlamlı farklılıklar bulunmuştur ($p<0.05$). Kan SUPAR için kesme değeri 136.61ng/L idi.

Sonuç: Akciğer malignitesi olan hastalarda yüksek kan SUPAR düzeyleri, tanı öncesi dönemde spesifik olmayan bir belirteç olarak kullanılabilir ve tanı sonrası olumsuz sonuçların tahmin edilmesinde prognostik bir belirteç olarak değerlendirilebilir.

Anahtar kelimeler: Bronkoalveolar sıvı, SUPAR, akciğer kanseri, tüberküloz.

INTRODUCTION

Bronchoalveolar lavage (BAL) is a minimally invasive diagnostic method widely used to obtain information about lower respiratory tract disorders. Although it provides valuable diagnostic information, especially in cases where other diagnostic methods such as clinical history, physical examination, and imaging are inadequate, the determination of reliable biomarkers in BAL fluid maintains its importance for the early diagnosis of lung diseases. Soluble urokinase plasminogen activator receptor (SUPAR) levels in BAL fluid and blood as early diagnostic markers for lung cancer and tuberculosis[1,2]. SUPAR is a protein released primarily by activated macrophages and neutrophils. It serves as a biomarker of immune activation and has been shown to increase in the blood and BAL fluid during various infections, inflammatory conditions, and malignancies. Under normal circumstances, plasma SUPAR levels remain below 3 ng/mL in healthy individuals, but they can exceed 6 ng/mL in critically ill patients. Elevated SUPAR levels are associated with disease presence, severity, and progression, making it a promising tool for early diagnosis and prognostic assessment. Its involvement in processes such as inflammation, tissue remodeling, and immune regulation highlights its utility across a wide range of pathologies, including lung cancer and tuberculosis[3,4]. The evaluation of SUPAR levels in both blood and BAL fluid offers a novel approach to improving diagnostic accuracy and clinical outcomes in these high-morbidity diseases.

Lung cancer and tuberculosis (TB) are two of the diseases that receive extra attention because of their high morbidity and mortality rates. The current techniques of diagnosing these illnesses frequently result in delays in diagnosis and treatment, raising the risk of morbidity and mortality[5,6]. This study focuses on the potential of soluble urokinase plasminogen activator receptors (SUPAR) to differentiate tuberculosis and lung cancer from healthy individuals and other respiratory pathologies.

Despite the utility of BAL in diagnosing lower respiratory tract conditions, there is a notable gap in the literature regarding reliable biomarkers that can enhance early diagnosis,

particularly for lung cancer and tuberculosis. Both diseases present significant diagnostic problems since radiographic signs of tuberculosis are frequently mistaken for lung cancer symptoms (consolidations with irregular edges, thick-walled spaces, indicative of malignancy, etc.,), delaying treatment and misdiagnosing patients[3]. Furthermore, the existing diagnostic methods, such as sputum analysis and imaging, are not always sufficient, necessitating the exploration of additional markers like SUPAR. This study aims to address these gaps by evaluating the potential of SUPAR levels as a reliable biomarker that could expedite the diagnosis of these serious conditions[7,8].

The primary objective of this study is to investigate whether SUPAR levels in bronchoalveolar lavage fluid and blood samples can serve as early diagnostic markers for lung cancer and tuberculosis. Specifically, the study will assess the correlation between SUPAR levels and the presence, progression, and severity of these diseases, aiming to determine the diagnostic value of SUPAR as a serological marker that could improve early detection and clinical outcomes.

METHODS

Study Design

This prospective, single-center study was conducted in the Harran University. The protocol received approval from the Ethics Committee of Harran University (2021/04.13), and the study was conducted following the Declaration of Helsinki. All participants were informed, and written voluntary informed consent was obtained prior to participation.

Participants

The participants were recruited at the Clinical Laboratory of Chest Diseases and Thoracic Surgery Clinics. We include participants who had met the following inclusion criteria: (1) with pathology detected on AC imaging and who underwent bronchoscopy (2) >18 years, and (3) patients diagnosed with TB, AC cancer, or other AC pathologies after pathological and microbiological examinations. In total, 66 patients with diagnoses of pulmonary tuberculosis, lung cancer, and other respiratory conditions were included in the study. In addition, 30 healthy individuals (control group) with no known lung disease were included.

Outcome Measures

During the bronchoscopy procedure, simultaneous blood samples and BAL fluid samples were collected from each patient. The samples were immediately frozen and stored at -80 °C until analysis. The levels of SUPAR in the BAL fluid and blood samples were measured using the enzyme-linked immunosorbent assay (ELISA) method. The ELISA kits were used according to the manufacturer's instructions to ensure accurate and consistent results.

For comparison, blood samples were also collected from 30 healthy individuals who served as the control group.

Data Analysis

The SUPAR levels in the blood and BAL fluid samples from the patients were compared to the SUPAR levels in the blood samples from the healthy control group. A statistical analysis was performed to determine the significance of the differences in SUPAR levels between the groups.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) 22.0 software was used for statistical analyses. The Shapiro-Wilk test was applied to assess the normality of data distribution. Since the data followed a normal distribution, parametric tests were used. Demographic and baseline clinical differences between groups were analyzed using independent sample t-tests for continuous variables and the χ^2 test for categorical variables. One-way ANOVA was performed for comparisons among multiple

groups. A type I error level below 5% ($p < 0.05$) was considered statistically significant. Receiver Operating Characteristic (ROC) analysis was conducted to evaluate SUPAR levels, and the diagnostic performance was assessed using the area under the curve (AUC) values.

RESULTS

The study was conducted on a patient group (n = 66; 46 males, 20 females; mean age: 52.21) and a healthy control group (n = 30; 17 males, 13 females; mean age: 52.69). The patient group included individuals diagnosed with tuberculosis (TB) (n = 12), lung cancer (n = 14), and other respiratory diseases (n = 40). Bronchoalveolar lavage was collected from 66 patients participating in the study. Of these, 46 (69.69%) were male and 20 (30.31%) were female. As the control group, blood was taken from 30 healthy individuals, of whom 17 (56.7%) were male and 13 (43.3%) were female (Table 1). The mean blood SUPAR value of the patients was 229.59±79.03 ng/L. The large variation observed is attributed to the significant difference in blood SUPAR values between patients and healthy individuals. In healthy individuals, the mean was 108.20±2.14 ng/L. This was found to be statistically significant ($p<0.05$). The mean blood SUPAR value for the patient group was 121,381 ng/L higher than the control group. The cut-off value was found to be 136.61 ng/L. The blood SUPAR value was found to be statistically significant for the patients.

The mean blood SUPAR value of lung cancer cases was 199.40 ± 77.65 ng/L, while it was 246 ± 63.76 ng/L in tuberculosis. When SUPAR levels in the blood and BAL fluid were examined in terms of diagnoses, the BAL/blood SUPAR ratio was 0.34, 0.16, and 0.21 for lung cancer, tuberculosis, and other diseases, respectively.

When the diseases were compared, lung cancer was found to be statistically significant compared to other lung pathologies ($p < 0.01$) (Table 1).

Table I: Baseline characteristics of participants

	CA	TB	Others	Control	*p*
Age, years	60.36	44.75	52.98	52.69	0.47
Gender (male/female)	10/3	8/3	28/13	17/13	0.24
Blood SUPAR	199.4	246.09	234.59	108.20	0.001
BAL SUPAR	56.78	39.24	44.00	-	0.09
BAL/blood SUPAR ratio	0.34	0.16	0.21	-	0.01

TB: tuberculosis, CA: malignancy, SUPAR: soluble urokinase plasminogen activator receptor, BAL: bronchoalveolar lavage fluid

In the patient group, blood SUPAR levels showed a significant decrease with increasing age. Patients under 30 years had the highest blood SUPAR levels (264.81 ± 64.15 ng/L), followed by those aged 31-59 years (243.97 ± 86.78 ng/L), while patients over 60 years had the lowest values (203.63 ± 65.16 ng/L) ($p = 0.034$). This indicates a significant negative correlation between age and blood SUPAR levels in the patient group. (Table 2). Figure 1 illustrates the distribution of blood SUPAR values across different age groups, showing a decreasing trend with increasing age.

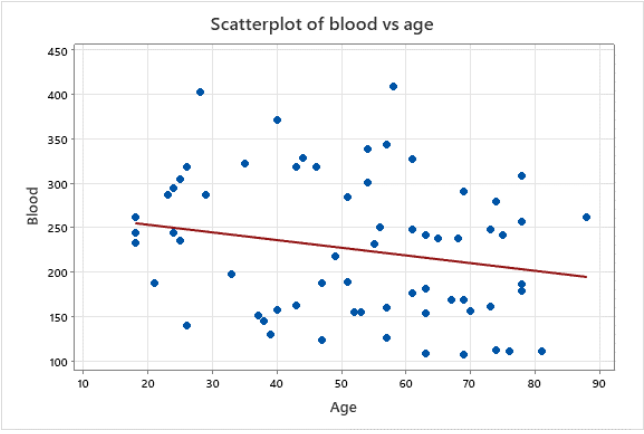

Figure 1. The blood SUPAR values with age in patients.

Table II: Comparison of blood SUPAR levels of the patients according to the groups

		Patient group blood SUPAR (ng/L)	*p*	Control group blood SUPAR (ng/L)	*p*
Age	*less than 30 years*	264,81±64,15	**0,034**	102,04±11,80	0,072
	31-59 years	243,97±86,78		105,06±10,96	
	more than 60 years	203,63±65,16		114,76±13,33	
Gender	*women*	240,32±71,53	0,588	108,22±12,10	0,674
	men	229,07±80,71		110,31±14,20	

Figure 2 presents the ROC curve analysis, demonstrating the diagnostic performance of blood SUPAR levels in distinguishing lung cancer from other diseases. ROC analysis was performed to assess the diagnostic potential of blood SUPAR levels. The area under the curve (AUC) values were 0.922 for lung cancer ($p < 0.001$, 95% CI: 0.830–1.000), 0.997 for tuberculosis ($p < 0.001$, 95% CI: 0.988–1.000), and 0.958 for other lung diseases ($p < 0.001$, 95% CI: 0.912–1.000). The optimal cut-off value for blood SUPAR was determined as 136.61 ng/L using Youden's index, which provided the best sensitivity and specificity in differentiating patient groups from healthy controls. These findings suggest that blood SUPAR levels have a high diagnostic potential for distinguishing between lung cancer, tuberculosis, and other lung diseases.

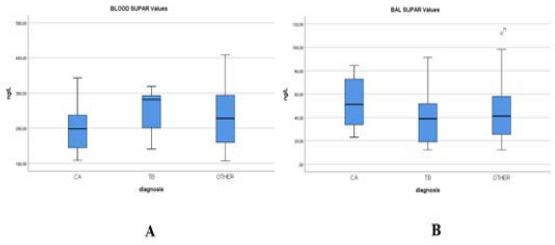

Figure 2. SUPAR values A) in the blood and B) BAL fluid of the patients.

DISCUSSION

We investigated the use of SUPAR levels in bronchoalveolar lavage and blood samples as an early and serological marker in the diagnosis of TB and lung cancer. We found that blood SUPAR level decreased with age (patients' blood SUPAR value 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. A significant difference was found between the blood SUPAR values in the patient and control groups. SUPAR values in BAL fluid were not statistically significant in these three lung pathologies.

Lung cancer is the leading cause of death from cancer. Urokinase plasminogen activator is present in the cell. It has a soluble form in the cell membrane and circulation. This allows both binding and activation of the urokinase plasminogen activator. It thus leads to the conversion of the plasmin gene to plasmin and the resulting proteolytic activity being 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[9]. Increased blood SUPAR levels in lung cancer cases are consistent with previous findings indicating that elevated SUPAR may reflect tumor activity and metastatic potential[10]. This supports its potential role as a biomarker in oncological settings. 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. The

diagnosis of lung cancer and pulmonary tuberculosis requires time. Early diagnosis is difficult. Early diagnosis of both diseases is important in terms of mortality and morbidity. It is 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[11-13]. We evaluated the contribution of the results obtained to the differential diagnosis of CA, TB, and other (interstitial lung disease, fungal infections, benign radiology) diseases by comparing the serum and BAL SUPAR values of CA, TB, and other cases with the serum SUPAR values of healthy subjects. We examined the question of whether there could be a fast, sensitive, and specific method for the early diagnosis of patients. Increases in serum SUPAR have been helpful in evaluating the invasion and metastasis processes of lung cancer[1]. SUPAR, as a promising biomarker, has been shown to be related to prognosis in patients with lung, breast, ovarian, and colon cancer with increased plasma levels[14-16].

It was observed that SUPAR increased in the blood in lung cancer cases, but it was not significant in the differential diagnosis of other diseases in the study. A comment could not be made because no comparison was made for BAL. Based on the BAL/blood SUPAR value 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 to the blood value 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[4,17-19].

SUPAR also contributes to diagnosis, like traditional biomarkers such as CRP and LDH[20-22]. Our findings suggest that while blood SUPAR has potential diagnostic and prognostic value, particularly in differentiating patient and control groups, the BAL/blood SUPAR ratio could provide additional insights into the assessment of cancer risk algorithms. Future studies should explore this ratio further in larger, homogeneous cohorts to validate its utility.

It was stated that SUPAR increased in the blood of individuals included in the study with age in some studies[4,23]. However, we found that the blood SUPAR level decreased with age, and it did not increase in the bronchoalveolar fluid. Our conclusion differs from their research. We considered our cohort as a heterogeneous group. In the form of lung cancer, TB, and other lung diseases. No significant difference was found in terms of gender and age in SUPAR values in both blood and BAL fluid, but the ratio of each other is valuable.

In our study, the blood SUPAR level was high in patients with lung cancer and was not specific. In a previous study, 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[11,24,25]. In our study, blood SUPAR levels were below the mean value in male and female patients with lung adenocarcinoma. The BAL-SUPAR value of women was found to be lower than the average SUPAR value. 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 whether the blood was low in the female population.

Limitations of the Study

Although blood SUPAR levels were high in male patients with adenocarcinoma in our study, several limitations should be noted. The limited number of patients and the heterogeneity of the diseases included in the study are significant

limitations. While providing some insight, the sample size of 66 patients may not be large enough to generalise the findings across broader populations. Additionally, the variety of diseases in the patient group (lung cancer, tuberculosis, and other lung diseases) introduces variability that could affect the interpretation of the results. Future studies with larger, more homogeneous patient groups are necessary to validate these findings and further elucidate the role of SUPAR in the diagnosis and prognosis of lung cancer and tuberculosis.

CONCLUSION

In this study, while blood SUPAR levels were lower in healthy individuals, they were elevated in patients with malignancy or other diseases. Elevated SUPAR levels can serve as a useful prognostic marker for predicting negative outcomes in the post-diagnosis period, even though they may be nonspecific in the pre-diagnosis period. Additionally, the study highlighted the need to explore whether there are differences in SUPAR levels among cancer subtypes and between genders, given that male patients with primary lung adenocarcinoma had above-average blood SUPAR values.

Moreover, the study concluded that SUPAR levels in bronchoalveolar fluid should be further investigated to understand their diagnostic and prognostic potential in lung cancer and tuberculosis. Future research should aim to clarify these findings and explore the utility of SUPAR in bronchoalveolar fluid for clinical applications.

Ethics Committee Approval: This prospective, single-center study was conducted in the Harran University. The protocol received approval from the Ethics Committee of Harran University (2017/1390), and the study was conducted following the Declaration of Helsinki.

Conflict of Interest: The authors declared no conflicts of interest.

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