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Original Research Paper

Surgery

DO PROINFLAMMATORY CYTOKINES SERVE AS DIAGNOSTIC OR PROGNOSTIC INDICATORS FOR TUMOR TYPE, STAGE, SIZE, STANDARDIZED UPTAKE VALUE, AND LYMPHOVASCULAR INVASION IN LUNG CANCER?

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ABSTRACT

Objectives: The number of human studies on the association and clinical significance of alterations in IL-6, sP-Selectin, TNF-α, BNP-32, or procalcitonin (PCT) in lung cancer is small. We aimed to investigate the alterations of proinflammatory cytokines and acute-phase reactants in blood and pleural fluid and determine their clinical diagnostic or prognostic significances regarding tumor type, stage, size, standardized uptake value (SUV), and lymphovascular invasion (LVI). **Methods:** Levels of IL-6, TNF-α, BNP-32, PCT, and sP-selectin were evaluated in blood samples obtained preoperatively and postoperatively on 1st, 6th hours and 1st, 4th, and seven th days. They also were evaluated in pleural fluid samples obtained postoperatively on 1st hour, and first and fourth days. These results were analyzed according to the cell type, size, stage, SUV, and LVI of lung cancer. **Results:** IL-6 values in plasma and pleural fluid had various significant relationships and correlations with histological type, diameter, SUV, stage, and LVI of the tumor. TNF-α values in plasma or pleural fluid had significant relationships with LVI only. PCT values in plasma or pleural fluid had significant relationships with the tumor's diameter, SUV, and LVI. BNP-32 values in plasma or pleural fluid had significant relationships with histological type and SUV of the tumor. sP-Selectin values in plasma or pleural fluid had significant relationships with the stage and SUV of the tumor. **Conclusions:** We determined various significant associations and correlations of proinflammatory cytokines with histological type, size, stage, LVI, and SUV of lung cancer. Studies on this subject would serve to develop diagnostic and prognostic methods in lung cancers.

KEYWORDS : Lung cancer - IL-6 - sP-Selectin - BNP-32 - TNF-α – procalcitonin

INTRODUCTION

Proinflammatory cytokines manifest various immune activities and have biological impacts in immunologically and inflammatory-mediated disorders and conditions such as trauma, surgery, and cancer, concurrent with acute-phase reactants. Increased synthesis of proinflammatory cytokines such as IL-6, IL-8, TNF-α, and lymphocytic proliferation occurs with increased acute-phase reactants such as procalcitonin. Such changes have been shown to induce phagocytosis, endothelial cellular activation, and reduction of the release of reactive oxygen species (ROS)[1-4].

IL-6 is among the multifunctional cytokines, released by T and B cells, monocytes, fibroblasts, keratocytes, endothelial cells, mesenchymal cells, adipocytes, and various tumor cells, and has active roles in the regulation of immune response, hematopoiesis, and inflammation [5, 6]. It was discovered in 1986, and since it was found to lead to the conversion of B cells to immunoglobulin-secreting B cells, it was first called the B-Cell Stimulant Factor (BSF-2)[6, 7].

Selectins are adhesion molecules released from the surfaces of activated platelets. They play roles in acute and chronic inflammation, together with tumor metastasis. The roles and relationships of selectins with lung have been rarely investigated[8-10].

TNF-α is a multifunctional cytokine as IL-6, and one of the cytokines activating the acute-phase reaction. It is an endogenous pyrogen, and its primary role is regulation of immune function; it is responsible for the inhibition of sepsis, systemic inflammation, apoptotic cell death, cachexia, tumor genesis, and viral replication. The other roles that TNF-α plays are hematopoiesis and inflammation[5].

Brain natriuretic peptide (BNP) is an inactive peptide released from the ventricular muscle due to myocardial cells' traction. It is a well-defined parameter for showing dysfunction of the left ventricle[11].

Procalcitonin (PCT) is the precursor of calcitonin, which is responsible for calcium homeostasis, and it is an acute-phase reactant and a proinflammatory cytokine. It has been well-known that its blood level increases in the presence of bacterial infection. PCT has a higher accuracy for differentiation of bacterial and non-infective inflammation compared to C-reactive protein[12].

The number of human studies that have been performed on the association and clinical significance of alterations in IL-6, sP-Selectin, TNF-α, BNP-32, or PCT in lung cancer is small. Inflammatory responses were reported in both local and systemic lung cancer [13]. Silva et al. recently reported that a high systemic IL-6 was associated with worse prognosis in patients with non-small lung cancer [14]. Shang et al., in their recent study, determined that IL-6 and TNF-α promoted metastasis in lung cancer via induction of epithelial-mesenchymal transition [15]. Pardo-Cabello et al. showed in their study that small cell lung cancer elevated PCT levels in the absence of infection [16]. Few studies have been published on the relationship between PCT and thoracic surgery [17, 18]. Zhao et al. investigated the discriminative values of C-reactive protein (CRP) and PCT between infectious fever and tumor fever, and determined that PCT level can discriminate tumor fever more accurately than CRP, and both PCT and CRP might predict different stages of lung cancer [19].

In this study, our hypothesis was that proinflammatory cytokines and acute-phase reactants would serve to indicate the type, stage, or lymphovascular invasion (LVI) of lung cancer. Thus, we aimed to investigate the alterations of proinflammatory cytokines and acute-phase reactants in blood and pleural fluid with the type, stage, size, standardized uptake value (SUV), and LVI of lung cancer and determine their clinical diagnostic or prognostic significances.

MATERIALS AND METHODS

Patients and Methods

A total of 34 patients aged older than 18 years who were planned to undergo surgery for lung cancer between April 2011 and December 2011 were included in the study. Patients with immunodeficiency and those receiving corticosteroids or immunosuppressive treatment were excluded from the study. None of the participants manifested fever or had empyema or signs of lower respiratory tract infection preoperatively.

Following approval of the study by the Ethics Committee of Adnan Menderes University Medical Faculty, the collection of the study data was initiated. All cases were informed about the study, and their written informed consent for participation in the study was obtained.

Patients' demographic data such as age and gender were recorded together with the type, stage, size, SUV of the tumor, and the presence of lymphovascular invasion. Those diagnosed with either squamous cell carcinoma (SCC) or adenocarcinoma (AdenoCA) were included in the study, and those diagnosed with other cancer types were excluded.

In the histological examination, when tumor cells were observed within lymphatic canals and vessels such as veins, venules, arteries, or arterioles, lymphatic vascular invasion (LVI) was recorded positive. Besides, identifying tumor emboli stained with hematoxylin-eosin (H-E) in peritumoral spaces lined with endothelium was considered positive for LVI.

Obtaining samples for laboratory measurements

Blood samples were collected preoperatively and postoperatively on the 1st hour, 6th hour, the first, fourth, and seventh days. They were rapidly transferred to the laboratory by the cold chain method for centrifugation and storage. Following placement into the safe-lock Eppendorf tubes, the samples were centrifuged, and then, the obtained serums were stored at -80°C until the time of analysis. The IL-6, TNF-α, BNP-32, PCT, and soluble P-selectin (sP-Selectin) serum samples' levels were measured using the commercial ELISA kits.

The pleural fluid samples were obtained postoperatively on the 1st hour, and the first and fourth days and placed into standard tubes. They were rapidly transferred to the laboratory by the cold chain method for centrifugation and storage. Following placement into the safe-lock Eppendorf tubes, the flexural fluid samples were centrifuged and then stored at -80°C until the time of analysis. The IL-6, TNF-α, BNP-32, PCT, and sP-Selectin levels in the pleural fluid samples were measured using the commercial ELISA kits.

Biochemical Analysis

***IL-6*:** IL-6 was studied using the commercial human IL-6 Platinum ELISA kit of eBioScience (Cat# BMS213/2). The assays were conducted according to the directives of the manufacturer. The ELISA plates were coated with anti-human IL-6 antibody. Coloring occurred with 3,3' 5' 5-tetramethylbenzidine, and absorption was measured at 450 nm according to the standard curves. The mean values were reported. The sensitivity for IL-6 was 0.92 pg/ml. The intra-assay and inter-assay coefficients of the variables were 3.4% and 5.2%, respectively.

Soluble P-Selectin (sP-Selectin): The p-Selectin soluble human ELISA kit of eBioScience (Cat# BMS219/4) was used for measuring the level of sP-Selectin. The assays were conducted under the instructions provided by the manufacturer. The ELISA plates were coated with anti-human P-Selectin antibody. Coloring occurred with 3,3' 5' 5-tetramethylbenzidine, and absorption was measured at 450 nm according to the standard curves. The mean values were reported. The sensitivity for P-Selectin was 0.2 ng/ml. The intra-assay and inter-assay coefficients of the variables were 7.8% and 5.4%, respectively.

TNF-α: The TNF alpha human ELISA kit of eBioScience (Cat# BMS223-4) was used for measuring the TNF-α level. The assays were conducted under the instructions provided by the manufacturer. The ELISA plates were coated with anti-human TNF-α antibody. Coloring occurred with 3,3' 5' 5-tetramethylbenzidine, and absorption was measured at 450 nm according to the standard curves. The mean values were reported. The sensitivity for TNF-α was 2.3 pg/ml. The intra-assay and inter-assay coefficients of the variables were 6% and 7.4%, respectively.

BNP-32: The BNP-32 human EIA kit manufactured by Phoenix Pharmaceuticals (Cat# EK-011-03) was used for measuring the BNP-32 level. This enzyme immunoassay kit was designed to scan for specific peptides and other related peptides according to the "competitive" enzyme immunoassay principle. The assays were conducted under the instructions provided by the manufacturer. Coloring occurred with 3,3' 5' 5-tetramethylbenzidine, and absorption was measured at 450 nm according to the standard curves. The coloring density was directly proportional to the amount of biotinylated peptide-SA-HRP complex but inversely proportional to the peptide amount in standard solutions and samples; this was a competitive binding of biotinylated peptide with peptide antibodies (primary antibody) or related standard peptides. The mean values were reported. The sensitivity for P-Selectin was 2.3 pg/ml. The intra-assay and inter-assay coefficients of the variables were $<10\%$ and $<15\%$, respectively.

Procalcitonin (PCT): The measurements of PCT were performed using the Procalcitonin kit manufactured by VIDAS® B·R·A·H·M·S Co. Instructions of the manufacturer were followed during measurements. The sensitivity for PCT was 0.09 ng/ml, and the intra-assay and inter-assay coefficients of the variables were 3.25% and 5.05%, respectively.

These results were analyzed according to the cell type, the size, and stage of lung cancer, the SUV level, and the presence

of lymphovascular invasion (LVI).

Statistical Analysis

The Statistical Package performed statistical analysis for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) version 23.0 software. Since the number of cases in all groups was less than 30, nonparametric tests (T-tests with two or more independent samples and the Kruskal-Wallis Test) were preferred to be used, and the mean values together with their standard errors were determined. Pearson's Correlation Coefficient was used for interpreting the presence of positive and negative correlations. A *p*-value of less than 0.05 was considered statistically significant, and these values were shown.

RESULTS

Thirty-four patients (32 males, two females) were determined to undergo surgery for lung cancer between April 2011 and December 2011 at XXXXXXXXXX Medical Faculty Hospital, Department of Thoracic Surgery. The mean age of the patients was 64.7±7.6 years, with a range between 47-79 years. The types and stages of lung cancer and lymphovascular invasion in the patients were presented in **Table 1.**

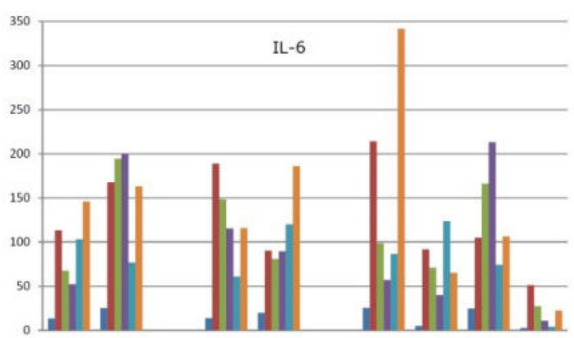
Table 1. Distribution of types and stages of lung cancer, the presence of lymphovascular invasion, the SUV and size of the tumor in patients with lung cancer (n=34)

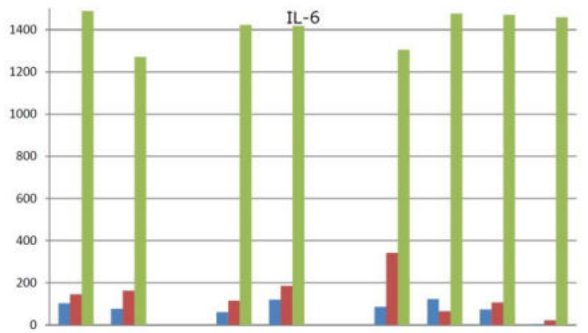
	n	%
Histological type		
Squamous cell	23	67.6
Adenocarcinoma	11	32.4
LVI		
Absent	14	41.2
Present	20	58.8
Tumor stage		
1	10	29.4
2	12	35.3
3	11	32.4
4	1	2.9
	Mean (Min-Max)	**Standard Deviation**
Tumor SUV	13.67 (2.50-31.00)	6.21
Tumor diameter (mm)	46.83 (4.00-100.00)	24.76

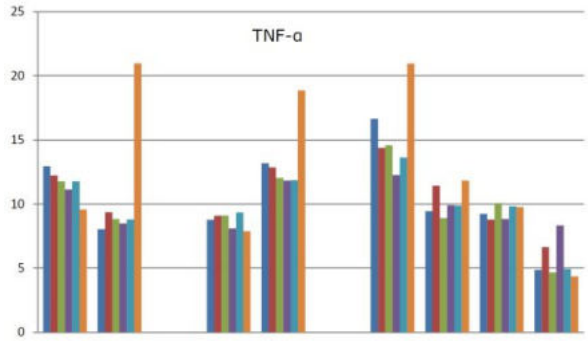
Distribution of cytokine levels according to the histological type of the tumor:

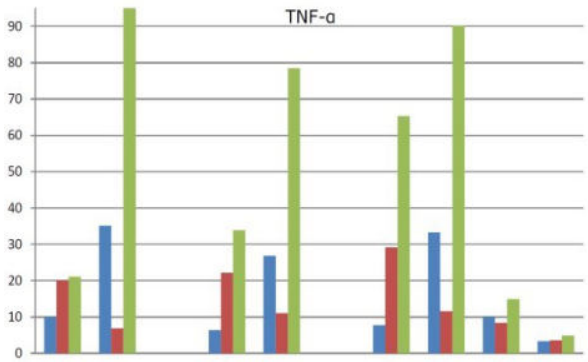
The distributions of cytokine levels according to the histological type of the tumor were shown in **Figure 1.**

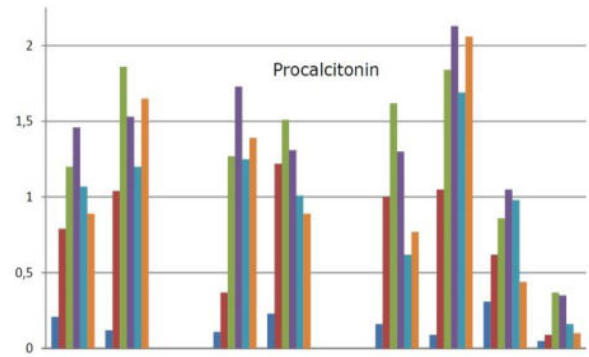
Figure 1. The distributions of IL-6, TNF-α, Procalcitonin, BNP-32, and sP-Selectin values in serum (A) and pleural fluid (B) over time according to tumor type, presence of lymphovascular invasion, and tumor stage

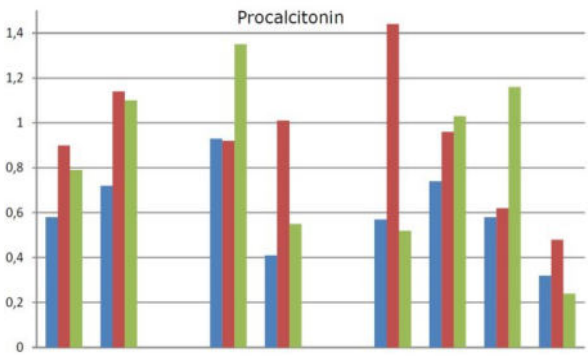


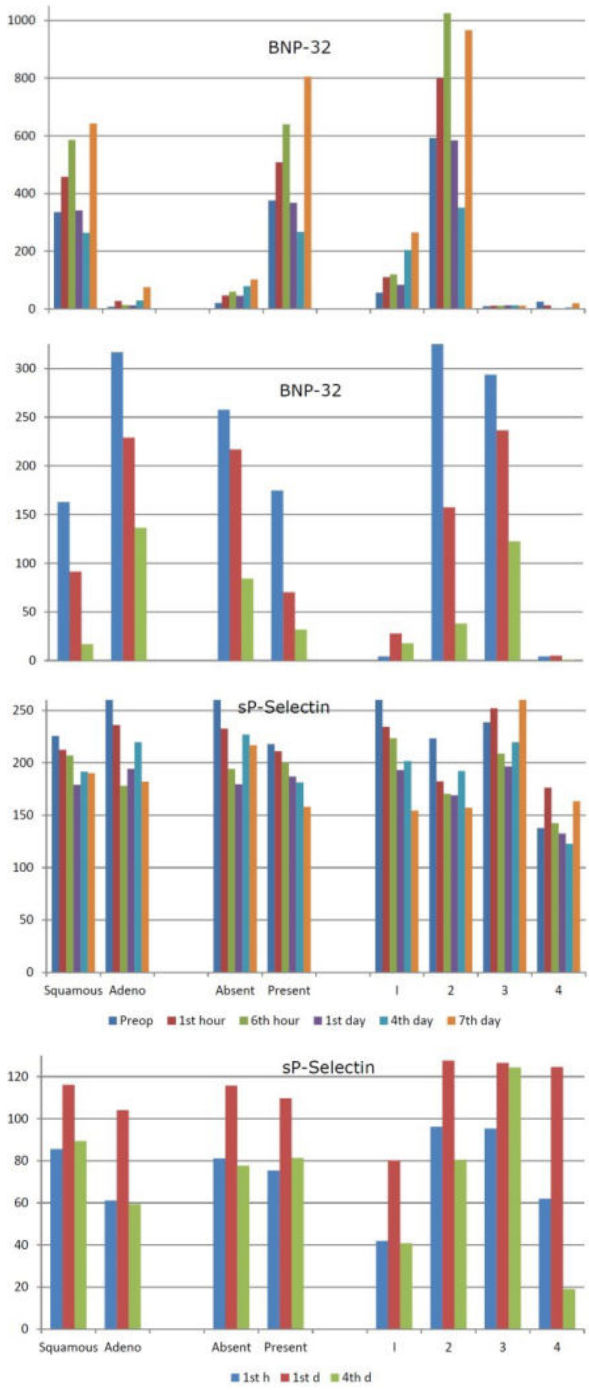












IL-6: The serum IL-6 level was significantly higher in patients with adenocarcinoma than those with squamous cell carcinoma on the first postoperative day (p=0.045). No other significant difference was present between squamous cell lung tumors and adenocarcinoma regarding IL-6 (p>0.05).

BNP-32: The preoperative serum BNP-32 value was significantly higher in patients with squamous cell lung cancer than those with adenocarcinoma (p=0.042). No other significant difference was present between squamous cell lung tumors and adenocarcinoma regarding BNP-32 (p>0.05).

No differences were present among the patient groups with squamous cell lung cancer and adenocarcinoma regarding the **sP-selectin, TNF**-α, and **procalcitonin** levels (p>0.05).

Distribution of cytokine levels according to the presence of lymphovascular invasion:

The distributions of cytokine levels according to the presence of lymphovascular invasion were shown in **Figure 1.**

IL-6: In the patient group with lymphovascular invasion, the postoperative 1st-hour serum IL-6 level was statistically significantly lower than the group with no LVI (p=0.020). No other significant difference was present between the cases with and without LVI regarding IL-6 (p>0.05).

Procalcitonin: In the patient group with lymphovascular invasion, the postoperative 4th-day pleural fluid procalcitonin level was statistically significantly lower (p=0.018) than the group with no LVI. No other significant difference was present between the cases with and without LVI regarding procalcitonin (p>0.05).

TNF-α: The postoperative 1st-hour pleural fluid TNF-α level was statistically significantly higher(p=0.005), and the postoperative 4th-day pleural fluid procalcitonin level was statistically significantly lower (p=0.018) when compared to the patient group with no lymphovascular invasion. No other significant difference was present between the cases with and without LVI regarding TNF-α.

No differences were present among the patient groups with squamous cell lung cancer and adenocarcinoma regarding the **sP-selectin** and **BNP-32** levels (p>0.05).

Distribution of cytokine levels according to the stage of the tumor:

The distributions of cytokine levels according to the stage of the tumor were shown in **Figure 1.**

IL-6: The preoperative serum IL-6 level was significantly lower in Stage 2 tumors than Stage 3 tumors (p=0.049). The postoperative 1st-hour serum IL-6 level was significantly higher in Stage I tumors than those in Stages 2 and 3 (p=0.018 and p=0.032, respectively). The postoperative 7th-day serum IL-6 level was significantly higher in Stage I tumors than in Stage 2 (p=0.019). No other significant difference was present between the tumor stages regarding IL-6 (p>0.05).

sP-Selectin: The postoperative 1st-hour serum sP-Selectin level was significantly lower in Stage 2 tumors than Stage 3 tumors (p=0.031). The postoperative 1st-hour pleural fluid sP-Selectin level was significantly lower in Stage I tumors than those in Stages 2 and 3 (p=0.008 and p=0.023, respectively). The postoperative 4th-day pleural fluid sP-Selectin level was significantly lower in Stage I tumors than those in Stages 2, 3, and significantly higher than Stage 4 (p=0.033, p=0.006, and p=0.009, respectively). No other significant difference was present between the tumor stages of the patients regarding sP-Selectin (p>0.05).

No significant differences were found between the patients' tumor stages regarding PCT, TNF-α, and BNP-32 (p>0.05).

Correlations between the Standardized Uptake Value (SUV) of tumors and the levels of proinflammatory cytokines:

IL-6: The tumor SUV and the first postoperative hour serum IL-6 value were negatively correlated (p= 0.0001, r= -0.681). No other correlations between the tumor SUV and the IL-6 level in serum or pleural fluid were determined.

PCT: The tumor SUV and the fourth postoperative day serum PCT value were positively correlated (p=0.045, r=0.422). No other correlations between the tumor SUV and the PCT level in serum or pleural fluid were determined.

sP-Selectin: The tumor SUV and the fourth postoperative day

pleural fluid sP-selectin value were positively correlated (p=0.001, r=0.652). No other correlations between the tumor SUV and the sP-Selectin level in serum or pleural fluid were determined.

BNP-32: The tumor SUV and the preoperative serum BNP-32 value were positively correlated (p=0.002, r=0.601). The tumor SUV and the postoperative 1st-hour serum BNP-32 value were positively correlated (p=0.002, r=0.591). The tumor SUV and the postoperative 6th-hour serum BNP-32 values were positively correlated (p=0.011, r=0.509). The tumor SUV and the postoperative 1st-day serum BNP-32 value were positively correlated (p=0.006, r=0.545). No other correlations between the tumor SUV and the BNP-32 level in serum or pleural fluid were determined.

TNF-α: The TNF-. level in serum or pleural fluid was neither negatively nor positively correlated with the tumor SUV.

Correlations between the tumor diameter and the proinflammatory cytokine levels in serum and pleural fluid:

IL-6: The tumor diameter and the fourth postoperative day pleural fluid IL-6 level were negatively correlated (p=0.036, r=-0.406). No other correlations between the tumor diameter and the IL-6 level in serum or pleural fluid were determined.

Procalcitonin: The tumor diameter and preoperative serum procalcitonin levels were positively correlated (p=0.025, r=0.409). No other correlations between the tumor diameter and the IL-6 level in serum or pleural fluid were determined.

The **TNF-α**, **BNP-32**, and **sP-Selectin** levels in serum or pleural fluid were neither negatively nor positively correlated with the tumor SUV.

DISCUSSION

In this prospectively conducted study, we investigated proinflammatory cytokines' associations with the type, SUV, size, and stage of the tumor, together with the presence of lymphovascular invasion in patients who were operated on for lung cancer. We determined that IL-6, BNP-32, procalcitonin, sP-Selectin, and TNF-α had various significant correlations and associations with the mentioned parameters at various time points.

The histological type of the tumor

The significantly increased blood IL-6 level on the first postoperative day in the patient group with adenocarcinoma compared to the group with squamous cell lung cancer may be due to the possibility that manipulation of adenocarcinoma caused an increased amount of IL-6 secretion during surgery when compared to squamous cell carcinoma. Another possibility is that the manipulation of squamous cell carcinoma might have led to a release of mediators that can suppress the IL-6 response.

The increase observed in serum BNP-32 value in the patient group with squamous cell lung cancer compared to the patient group with adenocarcinoma started as statistically significant for the preoperative value. Even though not statistically significant, the high trend for squamous cell cancer (SCC) group continued in all measurements. On the contrary, even though not statistically significant, the adenocarcinoma group's pleural fluid levels were higher than the Adenocarcinoma group in all measurements.

A literature search revealed no study comparing the level of BNP-32 between squamous cell lung cancer and adenocarcinoma. However, various studies related to the relationship of lung cancer to BNP-32 were present. The study conducted by Aujollet et al. in 2010 reported that N-terminal pro-B-type natriuretic peptide might have been a biomarker of lung cancer; however, they had not specified the type of lung cancer [20]. Lafaras et al., in their study on patients with non-small cell lung cancer, reported that pro-brain natriuretic peptide was a sensitive biomarker for detecting cardiac metastases [21]. Masago et al. also reported an association between brain natriuretic peptide and distant metastases in patients with advanced non-small-cell lung cancer [22]. There were also reports about brain natriuretic peptide production by human small cell lung cancer cells and malignant mesothelioma cells [23, 24].

Lymphovascular invasion

The significant increase determined in the 1st-hour pleural fluid level of TNF-α in LVI's presence may be consistent with the study conducted by Lee et al. [25]; their study investigating pathological factors related to tumor cell invasiveness reported that the preoperative C-reactive protein (CRP) level was associated with LVI in resected non-small cell lung cancer. TNF-α, like other proinflammatory cytokines, has been known to stimulate CRP production. It would be logical to suggest that parallel to an increased CRP level in the study by Lee et al., TNF-α level would also increase in LVI.

On the other hand, significant reductions determined in both IL-6 and PCT in our study's various time points were not supportive as for TNF-α. Regarding PCT, we believe that different mechanisms were active for the lower trend of pleural **procalcitonin** in cases with lymphovascular invasion, and we suggest that ultrastructural studies should be conducted to identify these mechanisms. Regarding IL-6, since the 1st-hour plasma IL-6 was lower in (LVI+) cases than (LVI-) ones, we may suggest that tumors that led to LVI might have released suppressor mediators against IL-6 response or malignancies of cases with inadequate IL-6 response against trauma might have led to LVI.

Tumor stage

In our study, IL-6 and sP-Selectin were the only parameters with various inter-stage differences in various time-points. Regarding IL-6, the mean preoperative plasma level of Stage III tumors being significantly higher than that of Stages II tumors was consistent with the results of various studies; increased IL-6 levels were associated with worse prognosis and distant metastases in lung cancer, particularly in NSCLC [14, 15, 26].

On the other hand, we did not determine a similar result regarding stage I tumors. Our Stage I patients' plasma IL-6 levels showed a higher trend compared to those in Stages II and III. We may suggest that, with increasing stage, the early immune response against trauma might have been suppressed via the mediators released.

Regarding sP-Selectin, our results of inter-stage comparisons were more consistent with each other and also with previous studies. Roselli et al. reported that increased levels of both sP-Selectin and sE-Selectin were associated with squamous lung cancer at late stages and were independently related to tumor stage by stepwise logistic regression analysis [27]. Xu et al. reported similar results for human p-Selectin in adenocarcinoma; the expression of p-Selectin in stages III and IV was significantly higher than its expression in stages I and II [28]. In our study, similar results were obtained; when a significant inter-stage difference was determined to be present regarding sP-Selectin, it favored increasing with patients' tumor stage.

SUV

Strongly positive correlations were determined between SUV and the plasma BNP-32 values measured at various time points starting preoperatively, giving us an idea that the more active the tumor, the more severe the degree of cardiac

dysfunction was. Another positive correlation was between SUV and the 4th-day pleural fluid sP-Selectin value, suggesting that adhesive activity increased with increasing tumor activity. SUV was strongly negatively correlated with the 1st-hour plasma IL-6 value. We may suggest that, with increasing the tumor's activity, the early immune response against trauma might have been suppressed via the mediators released. However, we could not find any study on the correlations between SUV and proinflammatory cytokines to discuss our results in light of the literature.

Tumor diameter

In our study, we determined a positive correlation between the tumor size and PCT; we found that, with increasing diameter of the tumor, the preoperative plasma PCT level increased also. Even though PCT has been known to increase mainly in bacterial infections, various studies have reported the presence and even PCT's biosynthesis in lung cancers, independent from infection [16, 29, 30]. However, we were unable to find a study investigating the association of tumor size with proinflammatory cytokines to discuss our results in the light of literature. We suggest that the increase determined in the preoperative level of procalcitonin with increasing tumor diameter might be due to tumor enhancing the inflammatory activity itself, or increased probability of developing obstructive pneumonia in larger tumors, and the presence of pneumonia activating procalcitonin.

An equally strong but negative correlation was determined between the tumor size and the 4th day pleural fluid IL-6 level. We suggest that with increasing tumor size, the early immune response against trauma might have been suppressed more via the mediators released, leading to reduced levels of IL-6 in the pleural fluid. Since we could not find any study on this subject, we cannot discuss our results considering literature.

Study limitations and advantages

One of the limitations of our study was its sample size. We performed this study in a single-center, and the sample size was small for investigating the validity of such a hypothesis. Another limitation of the study was the lack of various groups to compare, such as a control which might have involved normal individuals, and other patient groups with infectious or rheumatic disorders. On the other hand, the study's prospective nature was to the advantage of the results in reflecting its strength.

CONCLUSION

In our study, we determined various significant associations and correlations of proinflammatory cytokines with the histological type, size, stage, SUV of the lung cancer, and the presence of lymphovascular invasion. Studies on this subject would serve to develop diagnostic and prognostic methods to use in lung cancers. Since the number of studies on this subject is small, further prospectively conducted large-sample or multi-center human studies are required.

Compliance with Ethical Standards

***Conflict of Interest*:** All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

***Ethical approval*:** All procedures performed in studies involving human participants were following the ethical standards of the institutional research committee (Ethics Committee of Adnan Menderes University Medical Faculty) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was received before involvement in this study.

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REFERENCES

[1] Craig SR, Leaver HA, Yap PL, Pugh GC, Walker WS. *Acute phase responses following minimal access and conventional thoracic surgery*. Eur J Cardiothorac Surg 2001;**20**:455-63.
[2] Atwell DM, Grichnik KP, Newman MF, Reves JG, McBride WT. *Balance of proinflammatory and antiinflammatory cytokines at thoracic cancer operation*. Ann Thorac Surg 1998;**66**:1145-50.
[3] Endo S, Sato Y, Hasegawa T, Tetsuka K, Otani S, Saito N *et al. Preoperative chemotherapy increases cytokine production after lung cancer surgery*. Eur J Cardiothorac Surg 2004;**26**:787-91.
[4] Hoheisel G, Izbicki G, Roth M, Chan CH, Reichenberger F, Schauer J *et al. Proinflammatory cytokine levels in patients with lung cancer and carcinomatous pleurisy*. Respiration 1998;**65**:183-6.
[5] Akira S, Hirano T, Taga T, Kishimoto T. *Biology of multifunctional cytokines: IL 6 and related molecules (IL 1 and TNF)*. FASEB J 1990;**4**:2860-7.
[6] Mihara M, Hashizume M, Yoshida H, Suzuki M, Shiina M. *IL-6/IL-6 receptor system and its role in physiological and pathological conditions*. Clin Sci (Lond) 2012;**122**:143-59.
[7] Hirano T, Yasukawa K, Harada H, Taga T, Watanabe Y, Matsuda T *et al. Complementary DNA for a novel human interleukin (BSF-2) that induces B lymphocytes to produce immunoglobulin*. Nature 1986;**324**:73-6.
[8] Ortmann C, Brinkmann B. *The expression of P-selectin in inflammatory and non-inflammatory lung tissue*. Int J Legal Med 1997;**110**:155-8.
[9] Osaka D, Shibata Y, Kanouchi K, Nishiwaki M, Kimura T, Kishi H *et al. Soluble endothelial selectin in acute lung injury complicated by severe pneumonia*. Int J Med Sci 2011;**8**:302-8.
[10] Schutzman LM, Rigor RR, Khosravi N, Galante JM, Brown IE. *P-Selectin Is Critical for De Novo Pulmonary Arterial Thrombosis Following Blunt Thoracic Trauma*. J Trauma Acute Care Surg 2019;**86**:583-91.
[11] Sullivan DR, West M, Jeremy R. *Utility of brain natriuretic peptide (BNP) measurement in cardiovascular disease*. Heart Lung Circ 2005;**14**:78-84.
[12] Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. *Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis*. Clin Infect Dis 2004;**39**:206-17.
[13] De Vita F, Orditura M, Auriemma A, Infusino S, Catalano G. *Serum concentrations of proinflammatory cytokines in advanced non small cell lung cancer patients*. J Exp Clin Cancer Res 1998;**17**:413-7.
[14] Silva EM, Mariano VS, Pastrez PRA, Pinto MC, Castro AG, Syrjanen KJ *et al. High systemic IL-6 is associated with worse prognosis in patients with non-small cell lung cancer*. PLoS One 2017;**12**:e0181125.
[15] Shang GS, Liu L, Qin YW. *IL-6 and TNF-alpha promote metastasis of lung cancer by inducing epithelial-mesenchymal transition*. Oncol Lett 2017;**13**:4657-60.
[16] Pardo-Cabello AJ, Manzano-Gamero V. *Small cell lung cancer elevates procalcitonin levels in the absence of infection*. Lung Cancer 2019;**134**:272-73.
[17] Hoksch B, Fahrner R, Alexander Schmid R. *Procalcitonin and brain natriuretic peptide as parameters in the postoperative course of patients with major pulmonary resection*. Interact Cardiovasc Thorac Surg 2007;**6**:155-9.
[18] Franke A, Lante W, Kupser S, Becker HP, Weinhold C, Markewitz A. *Procalcitonin levels after different types of conventional thoracic surgery*. The Thoracic and cardiovascular surgeon 2008;**56**:46-50.
[19] Zhao Z, Li X, Zhao Y, Wang D, Li Y, Liu L *et al. Role of C-reactive protein and procalcitonin in discriminating between infectious fever and tumor fever in non-neutropenic lung cancer patients*. Medicine (Baltimore) 2018;**97**:e11930.
[20] Aujollet N, Meyer M, Cailliod R, Combier F, Coignet Y, Campard S *et al. High N-terminal pro-B-type natriuretic peptide: a biomarker of lung cancer?* Clin Lung Cancer 2010;**11**:341-5.
[21] Lafaras C, Mandala E, Saratzis A, Platogiannis D, Barbetakis N, Papoti S *et al. Pro-brain natriuretic peptide is a sensitive marker for detecting cardiac metastases in patients with non-small cell lung cancer*. Onkologie 2009;**32**:389-92.
[22] Masago K, Fujita S, Togashi Y, Irisa K, Sakamori Y, Hatachi Y *et al. Association between brain natriuretic peptide and distant metastases in advanced non-small cell lung cancer patients*. Oncol Lett 2011;**2**:253-56.
[23] Ohsaki Y, Gross AJ, Le PT, Oie H, Johnson BE. *Human small cell lung cancer cells produce brain natriuretic peptide*. Oncology 1999;**56**:155-9.
[24] Tsolaki V, Zarogiannis S, Zygoulis P, Kalomenidis I, Jagirdar R, Makris D *et al. Malignant mesothelioma cells secrete natriuretic peptides: Data and diagnostic clinical implications*. Respirology 2020.
[25] Lee JG, Cho BC, Bae MK, Lee CY, Park IK, Kim DJ *et al. Preoperative C-reactive protein levels are associated with tumor size and lymphovascular invasion in resected non-small cell lung cancer*. Lung Cancer 2009;**63**:106-10.
[26] Wojcik E, Jakubowicz J, Skotnicki P, Sas-Korczynska B, Kulpa JK. *IL-6 and VEGF in small cell lung cancer patients*. Anticancer Res 2010;**30**:1773-8.
[27] Roselli M, Mineo TC, Martini F, Mariotti S, Ambrogi V, Spila A *et al. Soluble selectin levels in patients with lung cancer*. Int J Biol Markers 2002;**17**:56-62.
[28] Xu X, Li Q, Yang J, Li X, Gao S. *[A study on the correlation between P-selectin and lung cancer.]*. Zhongguo Fei Ai Za Zhi 1999;**2**:74-6.
[29] Soeroso NN, Tanjung MF, Afiani D, Pradana A, Tarigan SP, Wahyuni AS. *Procalcitonin Level in Non-Small Cell Lung Cancer Patients among Indonesian Population*. Open Access Maced J Med Sci 2018;**6**:2123-27.
[30] Patout M, Salaun M, Brunel V, Bota S, Cauliez B, Thiberville L. *Diagnostic and prognostic value of serum procalcitonin concentrations in primary lung cancers*. Clin Biochem 2014;**47**:263-7.