

Comparison of C-reactive Protein Levels in Patients With Lung Cancer and Chronic Obstructive Pulmonary Disease

Neringa Vagulienė¹, Marius Žemaitis¹, Skaidrius Miliauskas¹, Daiva Urbonienė²,
Brigita Šitkauskienė¹, Raimundas Sakalauskas¹

¹Department of Pulmonology and Immunology, Medical Academy, Lithuanian University of Health Sciences,

²Department of Laboratory Medicine, Medical Academy, Lithuanian University of Health Sciences, Lithuania

Key words: lung cancer; chronic obstructive pulmonary disease; C-reactive protein; chronic inflammation.

Summary. *Objective.* The aim of this study was to establish C-reactive protein (CRP) levels in serum of patients with lung cancer and chronic obstructive pulmonary disease (COPD) and evaluate the associations of CRP levels with clinicopathological characteristics.

Materials and Methods. In total, 140 persons were included in the study: 43 patients with lung cancer, 34 patients with lung cancer and COPD, 42 patients with COPD, and 21 healthy subjects. CRP analysis was performed with a serum protein analyzer using commercially available high-sensitivity reagent kits.

Results. The C-reactive protein levels were significantly higher in the lung cancer patients with or without COPD compared with the COPD patients or the control group (20.42 ± 1.95 and 22.49 ± 2.31 vs. 8.37 ± 0.91 and 2.49 ± 0.47 mg/L, respectively; $P < 0.01$). The patients with advanced lung cancer had higher CRP levels compared with the patients suffering from early stage lung cancer (23.11 ± 1.72 vs. 14.59 ± 2.23 mg/L, $P < 0.01$). The CRP levels were significantly higher in the patients with early stage lung cancer compared with the COPD patients (14.59 ± 2.23 mg/L vs. 8.37 ± 0.91 mg/L, $P < 0.05$). No association was found between CRP and histology, lung function, and smoking status in the patients with lung cancer.

Conclusions. Chronic inflammation plays an important role in both diseases: lung cancer and COPD. However, it seems that inflammation is more pronounced in patients with lung cancer, as the CRP levels were significantly higher in these patients than other groups.

Introduction

Lung cancer is the major cause of cancer-related mortality in both men and women worldwide (1). There is growing body of evidence that chronic inflammation plays an important role in carcinogenesis. Oxidative damage related to inflammation can lead to carcinogenesis via inactivation of mutations in tumor suppressor genes or posttranslational modifications in proteins that are involved in DNA repair. It is known that proinflammatory cytokines such as interleukin 1, interleukin 2, tumor necrosis factor alpha, and tumor growth factor are able to stimulate the production of C-reactive protein (CRP) and influence survival, growth, mutation, proliferation, differentiation, and migration of tumor cells (2). Several chronic inflammatory processes have been clearly associated with specific cancers, such as Crohn's disease with colorectal cancer, chronic pancreatitis with pancreatic cancer, and chronic obstructive pulmonary disease (COPD) with lung cancer (2). Lung inflammatory diseases

such as COPD are characterized by leukocytic infiltration of the airways that is regulated by a variety of mediators such as cytokines, chemokines, and adhesion molecules (3). The epidemiological studies have shown that COPD is an important risk factor for lung cancer. Smokers with moderate or severe COPD have a 1.3- to 4.9-fold increased risk of lung cancer compared with smokers without COPD (4). Lung cancer is found in 40%–70% of patients with COPD, particularly in severe disease, and is a common cause of death in patients with COPD (5). The most likely explanation for the increased risk of lung cancer in COPD is the presence of chronic inflammation with an increased production of growth factors and angiogenic factors. Cessation of smoking in COPD patients reduces, but does not eliminate, the risk of lung cancer probably because inflammation persists even after smoking cessation (6). Smoking is a risk factor for the development of COPD as well as lung cancer. The inflammatory mediators and intracellular signaling pathways are potentially rel-

Correspondence to N. Vagulienė, Department of Pulmonology and Immunology, Medical Academy, Lithuanian University of Health Sciences, Eivenių 2, 50028 Kaunas, Lithuania
E-mail: neringa.vaguliene@gmail.com

Adresas susirašinėti: N. Vagulienė, LSMU MA Pulmonologijos ir imunologijos klinika, Eivenių 2, 50028 Kaunas
El. paštas: neringa.vaguliene@gmail.com

evant in the pathogenesis link between COPD and lung cancer.

CRP is an acute-phase protein, which is produced in the liver in response to elevated cytokine levels after an inflammatory stimulus (7). The short serum half-life and relatively robust and reliable response to inflammation make CRP an ideal candidate marker for inflammation. Recently, it has been shown that “acute-phase response” is also seen in a variety of diseases, such as cardiovascular disease, diabetes, systemic inflammatory diseases, some autoimmune disorders, and cancer (8–9). CRP levels have also been used to predict cancer risk, detect cancer recurrence, and determine prognosis (10–13). The role of chronic inflammation in the pathogenesis of lung cancer and its relation to the processes in COPD are still not fully understood. The aim of this study was to evaluate the levels of CRP, which is the marker of inflammation in patients with lung cancer, compare them with those from patients with COPD, and consequently analyze the relations between the expression of CRP and clinicopathological characteristics of patients.

Material and Methods

Subjects. A total of 140 subjects were examined: 43 patients with lung cancer, 34 patients with lung cancer and stable moderate-to-severe COPD, 42 patients with stable moderate-to-severe COPD, and 21 healthy individuals at the Hospital of the Lithuanian University of Health Sciences Kauno Klinikos from April 2009 till December 2010. All the patients met a number of criteria. They had not used inhaled and systemic steroids at least 1 month before the study. None of the subjects showed signs of acute respiratory infection at least one month before the investigations. Subjects were excluded if they had a history of another malignancy or other diseases associated with systemic inflammation, such as rheumatoid arthritis, inflammatory bowel disease, or connective tissue disorders, as these diseases may influence serum CRP levels. Before the patients with lung cancer received anticancer therapy, their clinical stage, tumor type, and performance status determined according to the Eastern Cooperative Oncology Group (ECOG) (14) were recorded at the time of diagnosis. The stage was determined according to the *TNM Classification of Malignant Tumours*, the sixth edition (15). The patients with lung cancer were divided into two groups according to the stage: early lung cancer – patients with stage I–II cancer, and advanced lung cancer – patients with stage III–IV cancer. COPD was diagnosed according to the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (16). The COPD patients were clinically stable (no exacerbation

during the previous 2 months) at the time of examination. All the COPD patients were screened for the deficiency of alpha-1 antitrypsin (AAT), and none of the patients had Z allele, which may cause genetically determined deficiency of AAT.

The study subjects were divided into 3 categories according to their smoking status: smokers, currently smoking persons with a smoking history of more than 10 pack-years; ex-smokers, individuals with a smoking history of more than 10 pack-years who had ceased smoking more than 2 years before the study; and never-smokers, individuals who have never smoked. To calculate pack-years of smoking, the total number of years of smoking was multiplied by the average number of cigarettes smoked per day and divided by 20 (years \times cigarettes per day/20).

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

The Kaunas Regional Ethics Committee for Biomedical Research approved the study, and written informed consent was obtained from all participants.

Lung Function Testing. Lung function was measured by spirometry using a pneumotachometric spirometer “Custo VitM” (Custo Med, Munchen, Germany) with subjects in the sitting position, and the highest value of forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) from at least two technically satisfactory maneuvers differing by less than 5% was recorded. Predicted values were obtained from Quanjer et al. (17). The subjects had to avoid the use of short-acting β_2 -agonists at least 8 hours prior the test.

CRP Measurement. Peripheral venous blood samples were taken before receiving anticancer therapy. Serum CRP levels were measured using high-sensitivity CRP reagent kits (Dade Behring, USA) with a protein analyzer BNTM100 N. The lower detection limit was 0.15 mg/L. Serum levels of ≤ 3.10 mg/L were defined as normal.

Statistical Data Analysis. Statistical data analysis was performed using the statistical SPSS for Windows 18.0 software package. The data are presented as mean \pm standard error of the mean and medians, with ranges. The categorical data were compared using the chi-square test. Differences among all the study groups (more than two groups) were evaluated using the Kruskal-Wallis test. Differences between two groups were evaluated using the Mann-Whitney *U* test. The association between serum CRP level and clinicopathological characteristics was measured by the Spearman correlation coefficient. Statistical significance was set at $P < 0.05$.

Results

The characteristics of the study population are described in Table 1. All the investigated groups

Table 1. Clinical Characteristics of the Study Population

Variable	Patients With Lung Cancer n=43	Patients With Lung Cancer and COPD n=34	Patients With COPD n=42	Healthy Individuals n=21
Gender, n (%):				
Male	36 (83.7)	30 (88.2)	37 (88.1)	16 (76.2)
Female	7 (16.3)	4 (11.8)	5 (11.9)	5 (23.8)
Age, mean±SEM, years	62.2±1.4	64.8±1.1	65.3±1.2	61.0±1.3
BMI, mean±SEM, kg/m ²	27.6±0.4	26.9±0.4	28.9±0.7	29.3±1.4
Smoking, n (%):				
Never-smokers	6 (13.9)	4 (11.8)	8 (19.0)	6 (28.6)
Ex-smokers	14 (32.6)	14 (41.2)	17 (40.5)	7 (33.3)
Smokers	23 (53.5)	16 (47.0)	17 (40.5)	8 (38.1)
Smoking pack-years, median (range):				
Ex-smokers	29.0 (10–50)	37.5 (15–63)	38.0 (5–57)	25.5 (7–44)
Smokers	43.0 (15–70)	44.0 (20–104)	33.0 (15–94)	28.0 (13–56)
FEV ₁ , mean±SEM, % pred.	83.4±3.5*	51.3±2.5**	55.6±2.3**	109.1±4.3
FEV ₁ /FVC ratio, mean±SEM	95.5±1.7*	68.0±2.1**	76.6±2.2**	107.3±2.0

FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

* $P<0.05$, compared with lung cancer/COPD, COPD, and control groups. ** $P<0.05$, compared with lung cancer and control groups.

were matched for age, gender, BMI, smoking status, and smoking intensity. Elevated (>3.10 mg/L) serum CRP levels were observed more frequently in the lung cancer patients without (95.3%, 41/43) or with (94.1%, 32/34) COPD than in the patients with COPD (80.5%, 33/41) or in the control group (33.3%, 7/21) ($P<0.05$). The highest serum CRP levels were found in the groups of patients with lung cancer with or without COPD compared with the patients with COPD or control group (Fig. 1). The serum CRP levels in the patients with lung cancer did not significantly differ from those of the patients with lung cancer and COPD; therefore, these groups were merged into one for the further statistical analysis.

Serum CRP levels did not differ between the male and female patients with lung cancer (19.68 ± 2.12 mg/L vs. 24.21 ± 5.13 mg/L, $P>0.05$); lung cancer and COPD (22.67 ± 2.49 mg/L vs. 26.41 ± 12.74 mg/L, $P>0.05$); or control group (2.29 ± 0.52 mg/L vs. 2.48 ± 1.10 mg/L, $P>0.05$). In

the COPD group, serum CRP levels in the male patients were significantly higher than in the female patients (8.94 ± 0.96 mg/L vs. 3.18 ± 0.66 mg/L, $P<0.05$). There was no significant correlation between serum CRP levels and age or BMI in the investigated groups (data not shown).

The clinical characteristics of the patients with lung cancer are described in Table 2. There were no significant differences in serum CRP levels among the major lung cancer histologic types: adenocarcinoma, squamous cell carcinoma, large cell carcinoma, non-small cell lung cancer not otherwise specified, small cell lung carcinoma (18.59 ± 4.67 mg/L, 25.08 ± 2.38 mg/L, 21.06 ± 3.17 mg/L, 19.26 ± 8.72 mg/L, 18.72 ± 3.31 mg/L) as well as non-small cell lung cancer and small cell lung cancer groups (22.31 ± 1.76 mg/L vs. 18.72 ± 3.31 mg/L, $P>0.05$). That is why these groups were also merged for the further analysis.

Serum CRP levels were significantly higher in the patients with advanced lung cancer than those with early lung cancer (23.94 ± 1.93 mg/L vs. 16.45 ± 2.29 mg/L, $P<0.05$). The patients with early lung cancer had a significantly higher serum CRP level than the patients with COPD ($P<0.01$) (Fig. 2).

Additionally, serum CRP levels were found to be higher in the lung cancer patients with poor performance status, i.e., with performance status ≥ 2 compared with those with performance status 0–1 ($P<0.05$). In the lung cancer patients with good performance status, serum CRP levels were significantly higher than in the patients with COPD ($P<0.01$) (Fig. 3).

According to subjects' smoking status, there were no significant differences in serum CRP levels among the smokers, ex-smokers, and never-

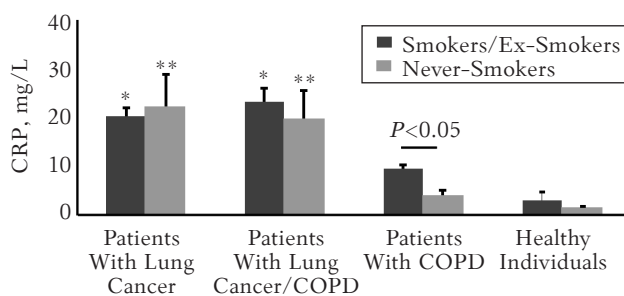


Fig. 1. Serum C-reactive protein (CRP) levels in smokers/ex-smokers and nonsmokers

Data are presented as mean±SEM.

* $P<0.05$, compared with COPD smokers/ex-smokers,

** $P<0.05$, compared with COPD never-smokers.

Table 2. Characteristics of Patients With Lung Cancer at the Time of Diagnosis

Variable	Patients, No. (%)
Lung cancer:	
NSCLC	62 (80.5)
SCLC	15 (19.5)
Histologic type:	
Squamous cell carcinoma	27 (35.1)
Adenocarcinoma	9 (11.7)
Large cell carcinoma	5 (6.5)
NSCLC-NOS	21 (27.3)
Small cell carcinoma	15 (19.5)
Stage of disease:	
Stage I	13 (16.9)
Stage II	3 (3.9)
Stage III	25 (32.5)
Stage IV	36 (46.8)
ECOG performance status:	
0	38 (49.4)
1	27 (35.1)
2	6 (7.8)
3	6 (7.8)

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; NSCLC-NOS, non-small cell lung cancer not otherwise specified; ECOG, Eastern Cooperative Oncology Group.

smokers in lung cancer groups without or with COPD ($P>0.05$). Serum CRP levels were significantly higher in the smokers and ex-smokers with COPD compared with the never-smokers with COPD (8.37 ± 1.51 mg/L and 10.30 ± 1.44 mg/L vs. 4.10 ± 0.86 mg/L, respectively; $P<0.05$). Additionally, serum CRP levels were found to be higher in the never-smokers with lung cancer with or without COPD compared with the never-smokers with COPD (23.43 ± 5.91 mg/L and 19.95 ± 5.72 vs. 4.10 ± 0.86 mg/L, respectively; $P<0.01$).

Serum CRP levels correlated with FEV_1 ($r=-0.609$, $P=0.001$), FEV_1/FVC ($r=-0.447$, $P=0.003$), and smoking intensity ($r=0.584$, $P=0.001$) in the patients with COPD. There was no significant correlation between serum CRP level and FEV_1 ($r=-0.203$, $P=0.192$), FEV_1/FVC ($r=0.113$, $P=0.469$), and smoking intensity ($r=-0.013$, $P=0.936$) in the group with lung cancer; between serum CRP level and FEV_1 ($r=0.005$, $P=0.976$), FEV_1/FVC ($r=-0.329$, $P=0.057$), and smoking intensity ($r=0.140$, $P=0.437$) in the group with lung cancer and COPD; and between serum CRP level and FEV_1 ($r=-0.282$, $P=0.290$), FEV_1/FVC ($r=-0.283$, $P=0.287$), and smoking intensity ($r=0.241$, $P=0.294$) in the control group.

Discussion

This study was designed to evaluate serum CRP levels in patients with lung cancer and COPD. It was found that the patients with lung cancer had an elevated level of inflammatory marker CRP in comparison with healthy subjects. As in many previous studies, higher serum CRP levels were also found in COPD patients compared with healthy

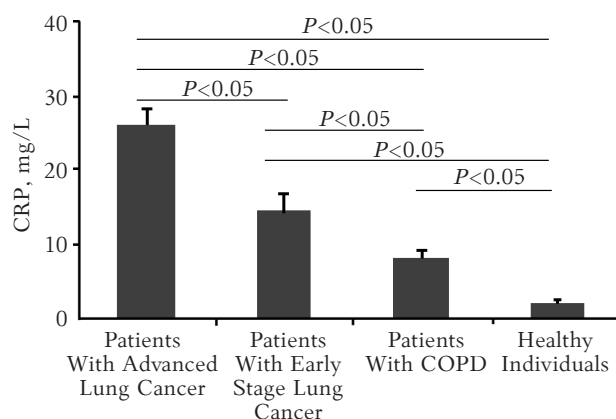


Fig. 2. Serum C-reactive protein (CRP) levels in patients with advanced and early stage lung cancer, patients with chronic obstructive pulmonary disease (COPD), and healthy individuals

Data are presented as mean \pm SEM.

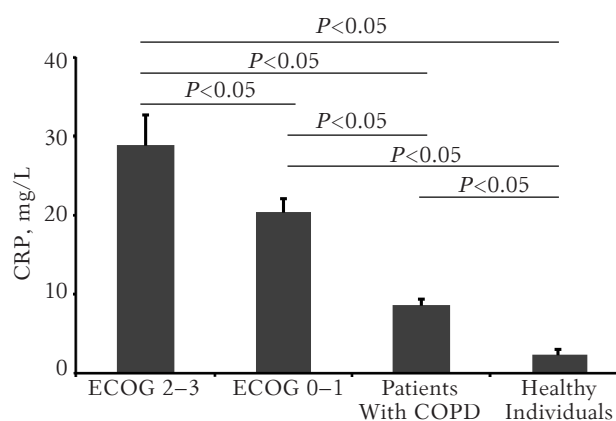


Fig. 3. Serum C-reactive protein (CRP) levels in lung cancer patients with poor and good performance status according to the Eastern Cooperative Oncology Group (ECOG), patients with chronic obstructive pulmonary disease (COPD), and healthy individuals

Data are presented as mean \pm SEM.

subjects (18–19). Furthermore, in previous studies, CRP levels have been found to be highly elevated in patients with cancer compared with healthy control subjects or subjects with benign conditions (8, 20), and recent studies have reported increased serum CRP levels in patients with advanced non-small cell lung carcinoma (21). These findings suggest that chronic inflammation plays an important role in pathogenesis of lung cancer and COPD (2–3). However, there are still insufficient data linking systemic inflammation in both diseases. To our knowledge, it is the first study analyzing serum CRP levels in lung cancer patients with and without COPD and comparing CRP levels with these of COPD patients and healthy subjects. This study demonstrated that serum CRP levels were higher in both lung cancer groups (lung cancer, lung cancer and COPD) than in the patients with COPD, but there were no differences between the lung cancer patients with

and without COPD. These data show that systemic chronic inflammation is probably more pronounced in lung cancer patients, but there is no additive effect in these two diseases consistent with those reported by other authors (22).

COPD is a disorder characterized by an abnormal local and systemic inflammatory response and is strongly associated with lung cancer (3–4, 23). Patients with lung cancer and COPD have an ongoing systemic inflammation, which can be assessed by measuring serum CRP. Several previous studies have suggested that increased serum CRP levels may predispose to the development of cancer (20, 24). It has been suggested that low-grade chronic inflammation may play a role in the pathogenesis of certain carcinomas. Elevated CRP concentrations are commonly observed in benign diseases (25), although there is also evidence that inflammatory lung diseases predispose individuals to lung cancer (26).

In our study, the patients with lung cancer and COPD did not differ in terms of age, gender, smoking status, or number of pack-years. Degree of airway obstruction did not differ between the lung cancer patients with COPD and COPD patients. BMI was also taken into account as it could increase CRP level. The systemic inflammation is associated with the development of cancer cachexia in patients with lung cancer (27). On the other hand, increased circulating levels of acute-phase proteins have been found to be associated with obesity (28). In this study, the average BMI did not differ in the patients with lung cancer and COPD. In this regard, it might be stated that the groups were well matched. However, no relationship between CRP and BMI was found in this study.

Lung cancer is classified to several histologic types, including small cell lung carcinoma and non-small cell carcinoma; the most common types of the latter are squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. Treatment and prognosis depend on the histologic type of lung cancer. A recent study has shown that a higher CRP level was associated with squamous cell carcinoma (29). No significant differences in serum CRP levels or frequency of elevated CRP (>3.10 mg/L) were found in our study among the major histologic types of lung cancer. Therefore, the hypothesis is raised that chronic inflammation is an early and universal process generating other alterations (including genetic) leading to lung cancer. It is necessary to address a few limitations to our study: the lung cancer analyses were based on a small number of lung cancer cases with different histologic types, which highlights the need for further larger prospective studies.

We also analyzed CRP levels in the patients with different stages of lung cancer (early vs. advanced). The patients with advanced lung cancer had higher

serum CRP levels than the patients with early stage lung cancer; the difference was statistically significant and consistent with that reported in other studies (21, 29) accounting for additional evidence of the importance of chronic inflammation in lung cancer progression. In order to evaluate the impact of primary lung cancer on chronic inflammation itself, serum CRP levels in the patients with early lung cancer without loco-regional spread or distant metastasis and COPD were compared. Our findings of significantly higher serum CRP levels in the patients with early lung cancer than in the patients with COPD further support our hypothesis that chronic inflammation can be more pronounced in the patients with lung cancer. Higher CRP levels were found in the lung cancer patients with poor performance status. Previous findings that systemic inflammatory response was associated with a reduction in performance status in the patients with lung cancer were also reinforced. This systemic inflammatory response is associated with a poor prognosis in both operable and advanced inoperable carcinoma (27).

Deregulated inflammation is complicit in the pathogenesis of COPD and lung cancer, but the overlap of signaling events is not fully understood yet. Cigarette smoking is established as the leading risk factor for lung cancer and COPD (5). There is a growing body of evidence that tobacco smoke exposure promotes widespread inflammatory and mutagenic effects in the lungs that promote a pro-cancer immune response (26). Recent studies have shown that CRP alterations and smoking status are independent prognostic factors for survival in patients with advanced non-small cell lung cancer (30, 31). However, the data on the influence of smoking itself on systemic inflammation in lung cancer patients with or without COPD are scarce. No difference in the mean CRP levels was observed between smokers, ex-smokers, and never-smokers with lung cancer with or without COPD. Although based on small numbers of studied subjects, our results suggest that inflammation due to other causes may be a relevant mechanism for lung carcinogenesis in never-smokers, too. Similarly, there was no difference between the patients with COPD who were current smokers and those who were ex-smokers (19). In contrast, never-smokers with COPD had significantly lower CRP levels than COPD smokers and ex-smokers. These findings may indicate the absence of an inflammatory response in smokers or persistent systemic inflammation in COPD patients even after smoking cessation, which is consistent with previous studies (18–19, 25). Our results showed that serum CRP levels in the nonsmoking patients with lung cancer with or without COPD were higher than in the nonsmoking patients with COPD and nonsmoking healthy subjects. These findings sup-

port the hypothesis that tumor can probably release inflammatory mediators and initiate chronic inflammation succession in nonsmoking patients with lung cancer. The study showed that smoking history (pack-years) positively correlated with serum CRP levels in the patients with COPD, but in the patients with lung cancer (with or without COPD), no correlation was observed. Such a relation once again supports the role of cigarette smoking in inflammatory response in patients with COPD (18–19). Smoking may be the initial determinant factor for chronic inflammation and can create an environment leading to cancerogenesis.

Conclusions

The present study demonstrated that serum C-reactive protein levels were significantly increased

in the patients with lung cancer compared with the patients with chronic obstructive pulmonary disease and healthy subjects. Patients with lung cancer often have chronic obstructive pulmonary disease, which suggests that there are commonalities in the pathogenesis of these diseases. Chronic inflammation plays an important role in both diseases – lung cancer and chronic obstructive pulmonary disease – but it seems that it is more pronounced in lung cancer patients. Finally, more detailed understanding of the role of chronic inflammation in the pathogenesis of lung cancer and chronic obstructive pulmonary disease may have an important clinical diagnostic and prognostic implication.

Statement of Conflict of Interest

The authors state no conflict of interest.

C reaktyviojo baltymo kiekis sergant plaučių vėžiu ir lėtine obstrukcine plaučių liga

Neringa Vagulienė¹, Marius Žemaitis¹, Skaidrius Miliauskas¹, Daiva Urbonienė²,
Brigita Šitkauskienė¹, Raimundas Sakalauskas¹

¹Lietuvos sveikatos mokslų universiteto Medicinos akademijos Pulmonologijos ir imunologijos klinika,

²Lietuvos sveikatos mokslų universiteto Medicinos akademijos Laboratorinės medicinos klinika

Raktažodžiai: plaučių vėžys, lėtine obstrukcinė plaučių liga, C reaktyvusis baltymas, lėtinis neinfekcinis uždegimas.

Santrauka. *Tyrimo tikslas.* Nustatyti C reaktyviojo baltymo kiekį kraujo serume pacientams, sergantiems plaučių vėžiu, plaučių vėžiu ir lėtine obstrukcine plaučių liga, lėtine obstrukcine plaučių liga bei nustatyti C reaktyviojo baltymo sąsajas su klinikinėmis ligų charakteristikomis.

Metodika. Tyrime dalyvavo 140 tiriamųjų: 43 sergantieji plaučių vėžiu, 34 sergantieji plaučių vėžiu ir lėtine obstrukcine plaučių liga, 42 sergantieji lėtine obstrukcine plaučių liga ir 21 sveikas asmuo. Įvertintas visų tiriamųjų C reaktyviojo baltymo kiekis kraujo serume.

Rezultatai. Sergančiųjų plaučių vėžiu bei plaučių vėžiu ir lėtine obstrukcine plaučių liga kraujo serume nustatytas didesnis C reaktyviojo baltymo kiekis nei sergančiųjų lėtine obstrukcine plaučių liga ir kontrolinės grupės asmenų ($20,42 \pm 1,95$ ir $22,49 \pm 2,31$ palyginti su $8,37 \pm 0,91$ ir $2,49 \pm 0,47$ mg/l, atitinkamai, $p < 0,01$). Sergančiųjų lokaliai ir sistemiškai išplitusiu plaučių vėžiu kraujo serume nustatytas didesnis C reaktyviojo baltymo kiekis nei sergančiųjų neišplitusiu plaučių vėžiu ($23,11 \pm 1,72$ palyginti su $14,59 \pm 2,23$ mg/l, atitinkamai, $p < 0,01$). Sergančiųjų neišplitusiu plaučių vėžiu kraujo serume nustatytas didesnis C reaktyviojo baltymo kiekis nei sergančiųjų lėtine obstrukcine plaučių liga ($14,59 \pm 3,36$ mg/l palyginti su $8,37 \pm 0,91$, atitinkamai, $p < 0,05$).

Išvados. Šio tyrimo duomenys rodo, kad galimai sergantiesiems plaučių vėžiu lėtinis neinfekcinis uždegimas yra labiau išreikštas nei sergantiesiems lėtine obstrukcine plaučių liga.

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