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The role of thiol/disulfide homeostasis in the differentiation of transudative and exudative pleural effusion

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Abstract

Aim: The dynamic thiol/disulfide homeostasis performs a major role in keeping up the oxidant-antioxidant equilibrium. We aimed to find the role of dynamic thiol/disulfide balance in pleural effusion transudate-exudate differentiation. This is considered to be the first research investigating the thiol/disulfide homeostasis in pleural fluid.
Materials and Methods: This prospective study was conducted in the Clinic of Chest Diseases of Training and Research Hospital. One hundred adult patients with pleural effusion included. 20-100 cc pleural fluid samples were taken through thoracentesis of the patients. These fluids were categorized as exudate and transudate according to Light's criteria. Automatic spectrophotometric practice which was defined by Erel & Neselioglu was used to gauge thiol/disulfide homeostasis in pleural fluid.
Results: Disulfide, total and native thiol levels were significantly higher in the exudative group than the transudative group (p = 0.001). The ratio of disulfide/native thiol and disulfide/total thiol was higher in the transudative group (p = 0.03). In exudates, native thiol/total thiol proportions were higher (p = 0.03).
Conclusion: The increased disulfide levels are indicative of increased oxidative stress in exudative pleural fluid. An abnormal thiol/disulfide state may be a major factor in the pathogenesis. These outcomes may conduce to distinguish exudative fluids without requesting synchronous serum thiol/disulfide level measurement.

Introduction

Pathologic amassment of fluid in pleural space is defined as pleural effusion and considered to be a frequent clinical problem (1). The incidence of is reported to be 3-5/1000 person-years. Although the reasons of pleural effusion differ between regions, congestive heart failure (CHF), tuberculosis, pneumonia and malignancy are responsible for three-quarters of cases (2). A rapid and systematic approach to diagnosis is essential in a patient with pleural effusion.

In all patients except for patients with clinically and radiologically highly probable heart failure and patients with minimal pleural effusion, thoracentesis should be performed at the initial stage before further examination (1). It is important for the pleural fluid to be defined as exudate or transudate following aspiration, for differential diagnosis, and for subsequent research and treatment planning. The most reliable diagnostic criteria for distinguishing exudative effusion from transudative effusion are known as Light criteria with an overall diagnostic accuracy of 95% (1, 2). Despite diagnostic thoracentesis, the etiology of pleural fluid may not be elucidated in 25% of patients (3). However, surgery procedures such as closed pleural biopsies, thoracoscopy or thoracotomy are required in significant percentage of patients with pleural effusion (4). Therefore, studies investigating less invasive methods such as pleural biomarkers are ongoing.

Oxidation of carbohydrates and fats is necessary to generate energy through metabolic events in organisms. In addition, exposure to ultraviolet rays, various chemical compounds, environmental pollution, smoking, infections and many factors such as diseases cause the formation of oxidative products, to prevent the harmful effects of these free radicals; there are a number of protection mechanisms that are effective both in the cell and in the cell membrane. Antioxidant defense systems are acting by eliminating the harmful effects of radicals and by preventing the radical production. The oxidative stress occurs when the protective mechanisms are insufficient or free oxygen radicals

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are increased (5).

Thiol which includes a sulfhydryl (-SH) group is an organic combination. This group plays a significant part in preventing oxidative stress in cells (6). Thiol/disulfide balance was previously investigated in respiratory system diseases such as community-acquired pneumonia (7), pulmonary thromboembolism (8), and the differential diagnosis of these respiratory system diseases (9). Because of the increased inflammation situation in the exudative pleural effusion, the oxidative stress indicators such as thiols are expected to be higher comparing with the transudate pleural effusion. There is no study in the literature, researching the thiol/disulfide homeostasis in the pleural effusion. In this study, our purpose was to show the role of thiol/disulfide balance in pleural effusion transudate-exudate diagnostic classification. We tried to find whether these oxidative stress indicators could help distinguishing the exudative pleural fluid from the transudate one.

Material and Methods

This single-centered, cross-sectional, prospective research was performed at the Training and Research Hospital Chest Diseases Clinic in January 2017 and October 2018. The research was authorized by the Ethics Council of Yildirim Beyazit University (26379996/143). One hundred patients with pleural effusion who were accepted to our clinic included in this study. Thoracentesis was applied to the participants who had no contraindications for the diagnostic thoracentesis procedure who accepted the informed consent form. The patients under 18 years of age, coagulopathy, pregnancy, presence of mental disability, with very little pleural effusion (less than 10mm) in radiological findings, with suspected tuberculosis (TB) and unwillingness to participate in the study were excluded from the study.

Demographic information, diagnosed diseases, medications used, history of occupation, exposure history, biomass exposure history and smoking history were recorded. Radiographic findings were recorded. In patients with moderate and massive amount of pleural effusions the appropriate area for thoracentesis was identified by physical examination, whereas the patients with a small amount of pleural effusion and the patients who were hospitalized in the pulmonary diseases clinic and/or intensive care unit were operated under the guidance of ultrasonography (USG), also thoracentesis in patients with loculated pleural effusion was performed with USG guidance.

Approximately 20-100cc pleural fluid specimens were obtained from patients with pleural fluid by thoracentesis. Blood samples were taken simultaneously with pleural fluid sampling. Total protein, lactate dehydrogenase (LDH), glucose and albumin grades were researched in pleural fluid and blood specimens. Adenosine deaminase (ADA) level, cell count, gram staining, Ziehl-Nielsen staining, nonspecific aerob culture, Lowenstein-Johnsen culture, tuberculosis polymerase chain reaction (PCR) and cytological examinations were also performed in pleural fluid. 4 cc samples from the pleural fluid was centrifuged at 3000 rpm and stocked at -80 °C until the study was carried out. These liquids were categorized as exudate and transudate with respect to Light criterion.

Thiol/Disulfide Homeostasis Measurement

Automatic spectrophotometric practice which was defined by Erel & Neselioglu was used to gauge thiol/disulfide homeostasis in pleural liquid. In this method, disulfide bonds are decreased together with sodium borohydride to form free functional thiol groups. The disused decreasing sodium borohydride was took out by consumption with formaldehyde to prohibit the degradation of 5,5'-dithiobis- (2-nitrobenzoic) acid (DTNB). The determination of total thiol groups (both native and reduced) were done after reaction with DTNB. 50% of distinction between native and total thiols obtained the dynamic disulfide content. Disulfide levels were calculated after total and native thiol levels were determined. Disulfide/native thiol, disulfide/total thiol and nativ thiol/total thiol ratios were found as percentages. Pleural effusions were categorized as exudate and transudate with respect to Light criterion. The main hypothesis of the study is: because of the increased inflammation situation in the exudative pleural effusion, the oxidative stress indicators such as Thiols are expected to be higher comparing with the transudate pleural effusion. So, in this study we tried to find whether these oxidative stress indicators can help distinguishing the exudative pleural fluid from the transudate one. As a secondary aim, differences in thiol-disulfide parameters were evaluated in etiologies causing pleural fluid formation.

Statistical Analysis

The statistical analysis was performed with the SPSS statistics software package, version 25.0 (IBM Corporation, Armonk, NY, USA). Dispersion homogeneity was measured using the Kolmogorov-Smirnov test and non-parametric tests were used because the data did not conform to the normal distribution. The Mann-Whitney-U test was used to make two variability comparisons. The Kruskal-Wallis variance test was used when more than two variables were compared. The correlations between pleural fluid LHD, protein, albumin, and thiol/disulfide homeostasis values were evaluated with Spearman's correlation coefficient. Continuous and discrete variables were summarized by median and interquartile range. Frequency (%) was given for categorical variables. Fisher's exact test was used to compare categorical variables between the groups. Results were interpreted according to $p < 0.05$ significance level.

Results

One hundred patients with pleural effusion were included in our study. Forty-three (43%) of the patients were female and 57 (57%) were male. The mean age was 70.4 years (20-96). When pleural effusion was evaluated with respect to Light criteria, cases were separated into two groups as transudate and exudate. Fifty patients (50%) were in the transudate and 50 (50%) were in the exudate group. Patients' demographic characteristics was compared and shown in Table 1. Among the causes of pleural effusion in the transudate group, the mostly seen disease was CHF.

Among the causes of the exudative pleural effusion, malignancies were the mostly seen diagnosis. In one CHF patient who underwent intensive diuretic therapy exudative pleural effusion was detected. Despite all the examinations performed in two cases in the exudate group, differential diagnosis could not be made. There were no cases of tuberculosis pleurisy among the causes of exudate, because there is no inpatient unit for active and/or resistant pulmonary tuberculosis patients. Patients with a high probability of pulmonary tuberculosis diagnosis are referred to hospitals with appropriate inpatient clinics for their treatment and follow-up (Table 2).

Table 1. Demographic characteristics of patients.

	Transudate (n = 50)	Exudate (n = 50)	p value
Age	(n, %)	(n, %)	
Mean (± SD)	74.8 ± 13.9	66.1 ± 14.3	0.002
Median(min-max)	77 (21-90)	67 (36-86)	
Gender, male	24 (48%)	33 (66%)	0.06
Smoking history	12 (24%)	27 (54%)	0.001

Table 2. Causes and frequency of transudate and exudative pleural effusion

Transudate (n = 50)	
Diagnosis	Frequency (n, %)
Congestive heart failure	34 (68%)
Renal failure	9 (18%)
Hypoalbuminaemia	6 (12%)
Nephrotic syndrome	1 (2%)
Exudate (n = 50)	
Diagnosis	Frequency (n, %)
Malignancy	30 (62.5%)
Parapneumonic	9 (18.8%)
Rheumatoid arthritis	3 (6.2%)
Pulmonary embolism	3 (6.2%)
Postoperative	2 (4.2%)
Congestive heart failure	1 (2.1%)
Without diagnosis	2 (4.2%)

Table 3. Distribution of pleural effusions according to radiological characteristics

	Transudate (n = 50)	Exudate (n = 50)	p value
Radiological localization			0.000
	(n, %)	(n, %)	
Unilateral: left	5 (10%)	15 (30%)	
Unilateral: right	17 (34%)	28 (56%)	
Bilateral	28 (56%)	7 (14%)	
Amount			0.122
Small	23 (46%)	19 (38%)	
Moderate	22 (44%)	18 (36%)	
Massive	5 (10%)	9 (18%)	
Localized	0 (0)	4 (8%)	

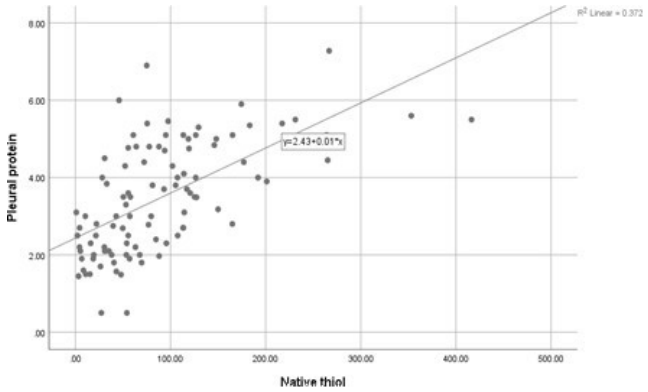

Figure 1. Positive correlation between the amount of protein in the pleural fluid and the native thiol.

After the radiological studies, bilateral effusion was observed in 28 (56%) patients with transudative pleural effusion and unilateral effusion was observed in 43 (86%) patients with exudative effusion (p = 0.000). A small to moderate amount of pleural effusion found in 45 (90%) patients with transudative effusion, and in 38 (74%) of the patients with exudative effusion (p = 0.122). In four of the patients (8%) in the exudate group, pleural fluid was localized as seen by thorax USG. Radiological features of pleural effusion are outlined in Table 3.

Thiol/disulfide levels in pleural fluid were evaluated and native and total thiol, and disulfide levels were significantly higher in the exudative effusion than in the transudate group (p = 0.000).

Disulfide/native thiol, disulfide/total thiol ratios were higher in the transudate group (p = 0.03). Native thiol/total thiol ratio was higher in the exudate group (p = 0.03) (Table 4).

The correlation between LDH, protein and albumin with thiol/disulfide homeostasis measurements were interpreted in the pleural fluid, a positive linear correlation was found between all parameters as showed in (Table 5). In exudative pleural effusions, the level of native thiol increased as the amount of protein increased, and the positive correlation was shown in Figure 1.

When evaluated according to the etiology causing pleural effusion formation, the highest native and total thiol levels were detected in parapneumonic effusion. The highest disulfide values were found in pleural fluid due to rheumatoid arthritis. The lowest native and total thiol and disulfide values were detected in a patient with nephrotic syndrome. In hypoalbuminemia and CHF, the parameters of thiol/disulfide balance were low (Table 6).

A statistically significant difference between CHF the most common cause of transudative pleural fluid and malignancies the most common cause of exudative effusion (p = 0.000) was found in all parameters of the thiol/disulfide hemostasis. Figure 2 shows the distribution of total thiol levels in CHF and malignant pleural effusion.

Discussion

In literature, the thiol/disulfide balance in pleural fluid has not been investigated before. This is considered to be the first research that investigates the thiol/disulfide balance. The first step to evaluate the etiology of the pleural effusion is to determine whether the effusion is transudative or exudative. In this research, the role of thiol/disulfide balance in differentia-

Table 4. Thiol/disulfide homeostasis values in transudative and exudative pleural effusions

	Transudate (n = 50)	Exudate (n = 50)	p value
Native thiol (μmol/L)	38.85 (36.80)	119.10 (72.10)	0.000
Total thiol (μmol/L)	50.00 (44.90)	146.05 (76.50)	0.000
Disulfide (μmol/L)	6.12 (5.30)	13.00 (6.10)	0.000
Disulfide / Native thiol	17.99 (25.10)	10.66 (7.73)	0.03
Disulfide /Total thiol	13.23 (12.67)	8.79 (5.05)	0.03
Native thiol/ Total thiol	73.54 (25.33)	82.95 (10.10)	0.03

Data shown as median and interquartile range (IQR).

Table 5. The correlation between thiol/disulfide homeostasis values with LDH, protein and albumin values.

Variable	LDH (g/dL)		Protein (g/dL)		Albumin (g/dL)	
	r	p-value	r	p-value	r	p-value
Total thiol (μmol/L)	0.704	0.000	0.694	0.000	0.683	0.000
Native thiol (μmol/L)	0.685	0.000	0.657	0.000	0.646	0.000
Disulfide (μmol/L)	0.559	0.000	0.593	0.000	0.617	0.000

Spearmans's r, p< 0.001, LDH: Lactate dehydrogenase

Table 6. Thiol/disulfide values according to pleural effusion etiology

Light	Diagnosis (n, %)	Native thiol	Total thiol	Disulfide
		Median (IQR)	Median (IQR)	Median (IQR)
Transudate	CHF(n = 34, 68%)	39.60 (40.90)	52.60 (42.80)	6.00 (4.10)
	Renal failure(n = 9, 18%)	40.50 (50.90)	68.90 (52.80)	3.60 (6.85)
	Hypoalbuminemia (n = 6, 12%)	27.20 (27.80)	30.20 (46.40)	8.75 (7.05)
	Nephrotic syndrome (n = 1, 2%)	10.80	17.80	3.50
Exudate	Malignancies (n = 30, 62.5%)	113.70 (48.40)	144.75 (55.80)	12.90 (6.75)
	Parapneumonic (n = 9, 18.8%)	192.00 (87.88)	220.00 (96.10)	14.90 (1.85)
	Rheumatoid arthritis (n = 3, 6.2%)	155.90 (90.30)	174.70 (51.00)	14.25 (24.50)
	PE (n = 3, 6.2%)	87.80 (55.10)	117.20 (54.90)	11.40 (3.40)
	Post-operative (n = 2, 4.2%)	122.25 (10.10)	141.20 (16.60)	9.48 (3.25)
	CHF (n = 1, 2.1%)	92.45	98.80	3.18

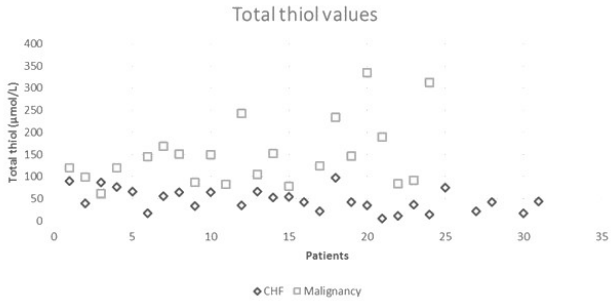

Figure 2. Total thiol values in pleural effusion caused by CHF and malignancy

tion of pleural effusion into exudates and transudates is evaluated. In exudative pleural effusion, native and total thiol and disulfide values were remarkably higher than transudate group (p = 0.000).

Nowadays, Light criteria are used as the most sensitive method in the diagnostic algorithm of pleural effusion. In the presence of at least one of the three Light criteria, pleural effusion is classified as exudate. Although the sensitivity of these criteria is quite high, their specificity is relatively low (1, 10). Approximately 20-25% of cases with transudative effusion may be misclassified in the exudative group; additional advanced examination and unnecessary invasive procedures may be performed. The need to examine the Light criteria simultaneously in both serum and pleural fluid may cause some disruptions related to the laboratory and the patient (11).

In the literature, there are studies conducted with many biomarkers other than Light criteria for the separation of pleural effusion transudate-exudate. Atalay et al's study, 113 patients with transudative and 246 patients with exudative pleural effusion; suggested that pleural ADA measurement is a reliable test with similar accuracy to protein and albumin gradi-

ent for exudate and transudate separation (12). Dikensoy et al. evaluated the level of ischemia-modified albumin in the pleural effusion and found a statistically remarkable increase in transudative fluid compared to exudate (p = 0.000) (13). The amino-terminal pro-brain natriuretic peptide (NT-proBNP) supports the diagnosis of decompensated heart failure with a specificity of 94% sensitivity 91% at the threshold of 1500 pg/ml in the pleural fluid. In particular, in 80% of misclassified cardiac effusions according to Light criteria, the levels of pleural fluid NT-proBNP were > 1500 pg/ml. The pleural fluid cholesterol level < 45 mg/dl defines the transudative effusion with a sensitivity of 85-90% and a specificity of 70-75% (14). In another study, the pleural fluid high density lipoprotein (HDL)/low density lipoprotein (LDL) ratio was found to be significantly higher in the transudates than the exudates (p = 0.001) and it was suggested that it could be used in pleural effusion separation without requiring serum level measurement (15).

Malondialdehyde as a sign of oxidative stress in the pleural fluid for exudate and transudate separation was investigated and found to be high in exudative fluids (16). In two different studies with superoxide dismutase (SOD) and SOD-2, an antioxidant enzyme, pleural fluid SOD and SOD-2 levels induced by tuberculosis were remarkably higher than patients with malignant pleural effusions (p < 0.05) and may be used to differentiate tuberculosis-related pleural fluid (17, 18). Tsilioni et al. evaluated pleural fluid 8-isoprostane and Cu/Zn SOD levels in transudate, malignant pleural effusion, tuberculosis, and parapneumonic effusion. While the Cu/Zn SOD levels of the pleural fluid were lower in transudes, serum levels were higher in the transudate group than in all exudative pleural effusions. 8-isoprostane level was higher in parapneumonic effusions than other groups (19).

In case of oxidative stress, the thiol/ disulfide balance may be disrupted and more native thiol oxidized (20). Low level of antioxidant capacity may increase cardiovascular diseases. Studies can be found showing that there is impaired thiol/disulfide balance in cardiovascular diseases (21, 22), pulmonary thromboembolism (8) and obstructive sleep apnea (23). Studies showing changes in dynamic thiol/disulfide balance have also been made in community-acquired pneumonia (7, 24). In all of these studies, the levels of native and total thiol were significantly decreased in the patients group compared with control group (p = 0.000). Serum disulfide levels were lower than in the control group in two studies conducted in patients with acute myocardial infarction (21) and obstructive sleep apnea (23) (p = 0.035, p = 0.039 respectively), in the other studies no statistical difference was found between study and control groups (7, 8, 21, 22, 24). In another study conducted in pediatric community-acquired pneumonia cases, disulfide levels were found to be low in pneumonia cases (p = 0.010). Disulfide/native thiol, disulfide/total thiol and native thiol/total thiol ratios were significantly higher in the pneumonia group (p = 0.001, p = 0.001, p = 0.001, respectively). It was reported that thiol/disulfide balance shifted to the direction of disulfide bond formation, and oxidative stress increased in community-acquired pneumonia (25). Two different studies with rheumatoid arthritis and ankylosing spondylitis showed that serum disulfide levels were remarkably higher than healthy control groups (26, 27). In another study of patients with lung cancer, serum native thiol, total thiol and disulfide levels were found to be low (28). In the literature, thiol disulfide parameters were evaluated in serum samples in all studies with thiol/disulfide homeostasis (7-9, 21-28). In this research, the thiol/disulfide homeostasis was evaluated in the pleural fluid. Serum and pleural fluid matrix are quite different from each other. Albumin thiols and protein thiols are the main ingredients in plasma thiol pool. In studies performed in lung cancer (28) and pneumonia (7, 24, 25) normal or low serum protein and albumin levels affect native and total thiol levels. The pleural effusion classified as transudate are caused by the failure of the balance of oncotic and hydrostatic pressure. Vascular structures, endothelium and pleural integrity were preserved. Since there is no inflammation, the liquid content is poor in protein and cells. In exudative pleural effusions, the permeability of the vessel wall increases due to inflammation; liquid protein and cell content is rich. Because of rised protein and albumin ingredients in exudative fluid, native and total thiol grades were found to be higher in our study than in other studies. Whereas the high levels of disulfide in the exudative effusion indicate that the antioxidant balance shifted to the direction of oxidative stress. Since the oxidized amount in the total thiol pool is showed by disulfide, this is because of the rise in reactive oxygen species. In this research, differences in thiol disulfide levels were observed according to the etiology of pleural effusion. The levels of disulfide in rheumatoid arthritis, parapneumonic effusion and malignant pleural effusion were quite high. The levels of disulfide in rheumatoid arthritis, parapneumonic effusion and malignant pleural effusion were found to be quite high. The lowest disulfide value was determined in one patient with nephrotic syndrome. Pleural fluid disulfide levels were found to be as low as the transudate group disulfide levels in a case with exudative pleural effusion due to heart failure.

There were some limitations affecting our study's findings. First of all, this study is a single-center, small-scale study. In the study methodology, the thiol/disulfide homeostasis was not evaluated in concurrent serum samples alongside with the pleural fluid. We have no results regarding the parameters of thiol/disulfide balance in tuberculosis pleurisy, since there is no inpatient unit for the follow-up of patients with active and/or resistant pulmonary tuberculosis in our hospital. Since no pleural fluid examination could be performed in healthy subjects, no such control group could be established.

Conclusion

In conclusion, we found that the grades of native and total thiol and disulfide were increased in exudative pleural effusion. These results may conduce to distinguish exudative effusions without requiring simultaneous serum thiol disulfide level measurement. With large-scale studies, the cut-off can be determined to differentiate between exudate and transudate. Rised disulfide levels are indicative sign of oxidative stress in exudative pleural fluid. We think that the large-scale, multicentre studies which contain enough number of patients with each etiology of pleural effusion using thiol disulfide parameters can help to distinguish specific causes of pleural effusion.

Ethical approval

Approval of the Ankara Yildirim Beyazit University Clinical Investigations Ethical Committee (2017/143) was obtained.

References

1. Feller-Kopman D, Light R. Pleural Disease. N Engl J Med 2018;378:740-51.

2. Porcel JM, Esquerda A, Vives M, et al. Etiology of pleural effusions: analysis of more than 3,000 consecutive thoracenteses. Arch Bronconeumol 2014; 50: 161–5.
3. Venekamp LN, Velkeniers B, Noppen M. Does 'idiopathic pleuritis' exist? Natural history of non-specific pleuritis diagnosed after thoracoscopy. Respiration 2005; 72: 74-8.
4. Metintaş M. Tanıda invaziv işlemler, İçinde: Metintaş M (editor). Plevra hastalıkları tanı ve tedavi rehberi, Bilimsel tıp yayınevi, 2016: 10-12.
5. Dean RT, Fu S, Stocker R, et al. Biochemistry and pathology of radical-mediated protein oxidation. Biochem J 1997; 324: 1–18.
6. Erel O, Neselioglu S. A novel and automated assay for thiol/disulphide homeostasis. Clin Biochem 2014; 47: 326-32.
7. Parlak E, Alisik M, Hezer H, et al. Evaluation of dynamic thiol/disulfide redox state in community-acquired pneumonia. Saudi Med J 2018; 39: 495-9.
8. Parlak E, Alisik M, Karalezli A, et al. Are the thiol/disulfide redox status and HDL cholesterol levels associated with pulmonary embolism? Thiol/disulfide redox status in pulmonary embolism. Clin Biochem 2017; 50: 1020–4.
9. Babaoglu E, Kılıc H, Hezer H, et al. Comparision of thiol/disulphide homeostasis parameters in patients with COPD, asthma and ACOS. Eur Rev Med Pharmacol Sci 2016; 20: 1537-43.
10. Lai J, Gouldstone A, Butler JP, et al. Relative motion of the lung and chest wall promotes uniform pleural space thickness. Respir Physiol Neurobiol 2002; 131: 233–43.
11. Light RW. Use of pleural fluid N-terminal-pro-brain natriuretic peptide and brain natriuretic peptide in diagnosing pleural effusion due to congestive heart failure. Chest 2009; 136(3): 656-8.
12. Atalay F, Ernam D, Hasanoglu HC, et al. Pleural adenosine deaminase in the separation of transudative and exudative pleural effusions. Clin Biochem 2005; 38: 1066-70.
13. Dikensoy O, Celik N, Kul S, et al. Ischemia modified albumin in the differential diagnosis of pleural effusions. Respir Med 2011; 105: 1712-7.
14. Porcel JM. Biomarkers in the diagnosis of pleural diseases: a 2018 update. Ther Adv Respir Dis 2018; 12: 1-11.
15. Köktürk O, Ulukavak Ciftci T, Firat H, et al. HDL/LDL ratio: a useful parameter for separation of pleural transudates from exudates. Tuberk Toraks 2005; 53: 34-9.
16. Papageorgiou E, Kostikas K, Kiropoulos T. Increased Oxidative Stress in Exudative Pleural Effusions: A New Marker for the Differentiation Between Exudates and Transudates? Chest 2005; 128: 3291-7.
17. Wang XF, Wu YH, Jiao J, et al. Diagnostic value of superoxide dismutase in tuberculous and malignant pleural effusions. Asian Pac J Cancer Prev 2013; 14: 821-4.
18. Wang M, Zhang Z, Wang X. Superoxide dismutase 2 as a marker to differentiate tuberculous pleural effusions from malignant pleural effusions. Clinics (Sao Paul) 2014; 69: 799-803.
19. Tsilioni I, Kostikas K, Kalomenidis I, et al. Diagnostic accuracy of biomarkers of oxidative stress in parapneumonic pleural effusions. Eur J Clin Invest 2011; 41: 349-56.
20. Turell L, Radi R, Alvarez B. The thiol poolin human plasma: the central contribution of albumin to redox processes. Free Radic Biol Med 2013; 65: 244-53.
21. Kundi H, Ates I, Kiziltunc E, et al. A novel oxidative stress marker in acute myocardial infarction; thiol/disulphide homeostasis. Am J Emerg Med 2015; 33: 1567-71.
22. Sivri S, Kasapkara HA, Polat M, et al. Dynamic thiol/disulphide homeostasis and its prognostic value in patients with non-ST elevation-acute coronary syndromes. Kardiol Pol 2018; 76: 426-32.
23. Argüder E, Parlak EŞ, Kılıç H, et al. Thiol-disulfide as a novel indicator of obstructive sleep apnea. Clin Respir J 2020; 14: 652-8.
24. Şener A, Çelik GK, Özhasenekler A, et al. Evaluation of dynamic thiol/disulfide homeostasis in adult patients with community-acquired pneumonia. Hong Kong J Emerg Med 2018
25. Solmaz A, Cevirgen B, Koyuncu I, et al. Investıgation of thiol-disulfide balance ın chıldren wıth pneumonıa. Ann Med Res 2020; 27: 2245-50.
26. Tuzcu A, Baykara RA, Omma A, et al. Thiol/Disulfide homeostasis in patients with rheumatoid arthritis. Rom J Intern Med 2019; 57: 30-6.
27. Baykara RA, Tuzcu A, Omma A, et al. Evaluation of serum thiol/disulfide homeostasis in patients with ankylosing spondylitis by a novel method. North Clin Istanb 2018
28. Dirican N, Dirican A, Sen O, et al. Thiol/disulfide homeostasis: A prognostic biomarker for patients with advanced non-small cell lung cancer? Redox Rep 2016; 21: 197-203.