Research Article

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Evaluation of pyruvate kinase and oxidative stress parameters in differentiation between transudate and exudate in pleural liquids

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Abstract

Objectives: We aimed to investigate the usability of pleural pyruvate kinase (PK), total antioxidant status (TAS), and total oxidant status (TOS) as an alternative to Light's criteria in exudate-transudate differentiation.

Methods: This prospective study was conducted among 84 patients (42 transudates and 42 exudates) with pleural effusion. The levels of PK, TAS, and TOS were measured by using ELISA kits, and the ROC analysis was used to evaluate the diagnostic efficiency.

Results: PK (p=0.001), TAS (p=0.027), and TOS (p=0.002) levels in pleural fluids were found to be significantly higher in the exudate group. The cut-off values for PK, TAS, and TOS were 10.64 U/L, 13.54 mmol trolox equivalent/L, and 13.88 μmol H_2O_2 equivalent/L, respectively. While the sensitivity values were 97.62 % for PK, 66.67 % for TAS, and 64.29 % for TOS, the specificity values were 80.95 % for PK, 52.38 % for TAS, and 57.14 % for TOS.

Conclusions: PK levels in pleural effusion can be useful in suspected cases to differentiate between exudate and transudate in addition to Light's criteria. However, pleural TOS and TAS parameters could not be as sensitive and specific as Light's criteria.

Keywords: pleural effusion; pyruvate kinase; total antioxidant status; total oxidant status; transudate-exudate

Introduction

Pleural effusion (PE) is described as the accumulated fluid in the pleural space. PE is divided into two categories: transudates and exudates [1]. Exudates are liquids, cells, or other cellular materials that slowly leak from blood vessels from inflamed tissues in general. Transudates are fluids that pass through a membrane or squeeze through tissue or into the extracellular space of tissues. Transudates are thin, watery, and contain few cells or proteins [2].

Currently, the most commonly used method in distinguishing between transudate and exudate PE has been reported as Light's criteria [3, 4]. The diagnosis of exudative PE is made in cases the fluid characteristics meet one of Light's criteria, which include a pleural/serum protein ratio >0.5, a pleural/serum lactate dehydrogenase (LDH) level >0.6, and a pleural LDH level over 2/3 of the reference value (or 200 IU) [5, 6]. It has been reported that Light's criteria identify 98 % of pleural exudates, and they misclassify about

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25 % of transudates as exudates [7]. Thus, there are various studies aimed to determine other parameters that can be used in the differentiation of transudates-exudates, especially with higher specificity for reducing the possibility of misclassification. It is crucial to distinguish between transudate and exudate for differential diagnosis and take appropriate action. For instance, the protein content of the pleural fluid is increased as a result of diuretic therapy, and it is misclassified as exudate in congestive heart failure patients with transudate pleural fluid [6, 7]. Therefore, new parameters such as serum-pleural fluid albumin gradient, pleural fluid cholesterol level, pleural fluid/serum cholesterol measurement, and Costa criteria have been reported in the distinction of transudate-exudate as an alternative to Light's criteria [8].

Pyruvate kinase (PK) is a well-known enzyme that catalyzes the conversion of phosphoenolpyruvate and adenosine diphosphate (ADP) to pyruvate and adenosine triphosphate (ATP) in glycolysis and plays a role in the regulation of cell metabolism [9]. PK and oxidative stress parameters [total antioxidant status (TAS) and total oxidant status (TOS)] have been examined directly or indirectly in the diagnosis of various diseases [10, 11]. However, to our knowledge, PK has not been tested in distinguishing between transudate and exudate in pleural liquids. Therefore, we have aimed to investigate the pleural PK and the oxidative stress parameters levels to differentiate between exudate and transudate as an alternative to Light's criteria.

Materials and methods

Patients who visited the Afyonkarahisar Health Sciences University Medical Faculty Hospital, Chest Surgery, and Chest Diseases Clinic between June 15, 2019, and December 1, 2020, were assessed. The study comprised 84 patients with PEs (42 transudates and 42 exudates as a result of distinction using Light's criteria).

The study included patients with pleural fluid aged 18 to 90 years. The study excluded patients who were younger than 18 years old, older than 90 years old, had bleeding diathesis and abnormal coagulation parameters, were unconscious, had hemothorax, chylothorax, empyema, pulmonary embolism, or had tuberculosis. It also excluded patients who were taking a diuretic, an antiplatelet, or an anticoagulant. After the physical examination, a chest X-ray and/or thorax computed tomography (CT) was taken. Thoracentesis was performed under sterile conditions, and two 20 mL fluid samples were taken into tubes separately from all patients with PE. Peripheral venous blood specimens were collected in serum vacuum tubes containing separator gel (volume of 8 mL) BD Vacutainer SST II advance (Becton Dickinson and Company Franklin Lakes, NJ, USA) simultaneously, and serum samples were obtained after centrifugation at 1,000 × *g* for 10 min. Afterward, two pleural fluid samples were centrifuged at 1,000 × *g* for 10 min, and only one pleura fluid sample for PK, TAS, and TOS was stored at –20 °C until analysis. Another pleura fluid and serum samples were studied in the biochemistry laboratory for albumin, total protein, LDH, glucose, total cholesterol, triglyceride, and low-density lipoprotein cholesterol (LDL-C) on biochemistry autoanalyzer Cobas c501 (Roche Diagnostics, Mannheim, Germany) including the parameters of Light's criteria. Moreover, a smear, nonspecific culture, acid-fast bacillus (ARB) staining, mycobacteria culture, and fluid cytology were examined in pleural fluid. In addition, albumin and protein gradients (respectively, serum albumin level-pleural fluid albumin level, serum protein level-pleural fluid protein level) were calculated.

According to Light's criteria, fluids were evaluated as exudate if at least one of the following three criteria was present and as transudate if none was present [7, 12].

- The ratio of pleural fluid protein to serum protein (protein P/S) is greater than 0.5
- The ratio of pleural fluid LDH to serum LDH (LDH P/S) is greater than 0.6
- Pleural fluid LDH and serum LDH greater than two-thirds of the upper limit of normal according to reference

The conclusive diagnosis was made in patients whose pleural fluid samples revealed exudative fluid, whose etiological cause was unknown, and who were suspected of having malignancy or granulomatous pleuritis by performing pleural biopsy by closed pleural biopsy or Video-Assisted Thoracoscopic Surgery (VATS) technique.

Analysis of PK levels in pleural fluid samples

PK levels of pleural fluid samples were measured by a microplate reader (BioTek, Epoch, Swindon-UK) using a specific ELISA kit (Bioassay Technology Laboratory, Shanghai, China). Linear detection ranges of the kit are 0.1–50 U/L for colorimetric assays and 0.01–2 U/L for fluorimetric assays run at 25 °C for 30 min in a 96-well plate. The detection limit of the kit is 0.01 U/L.

Analysis of TOS levels in pleural fluid samples

TOS was determined using a novel automated measurement method developed by Erel [13] (Rel Assay Diagnostic, Gaziantep, Turkey). Oxidants in the sample oxidize the ferrous ion-O-dianisidine complex to a ferric ion. The oxidation reaction is enhanced by glycerol molecules, which are abundantly present in the reaction medium. The ferric ion makes a coloured complex with xylenol orange in an acidic medium. The colour intensity, which can be measured spectrophotometrically, is related to the total amount of oxidant molecules in the sample. Briefly, 75 µL serum and 500 µL reagent 1 (H_2SO_4 25 mM, pH 1.75) were added to the test tube and stirred. 25 µL reagent 2 (H_2SO_4 25 mM, pH 1.75, ferrous ion 5 mM, and O-dianisidine 10 mM) were added to the mixture. The absorption of the solution at 660 nm was measured at 30 s (value A1) and 5 min (value A2) after mixing. The assay is calibrated with hydrogen peroxide, and the results are expressed in terms of µmol H_2O_2 equivalent/L for the pleural fluid sample.

Analysis of TAS levels in pleural fluid samples

TAS values were determined using a novel automated colorimetric measurement method developed by Erel [14] (TAS assay kit, Rel Assay Diagnostic, Gaziantep, Turkey). In this method, antioxidants in the

sample reduce the ABTS radical (dark blue-green) to a reduced ABTS form (colorless). The change of absorbance at 660 nm is related to the antioxidant level of the sample. A vitamin E analog, traditionally named Trolox equivalent, is used for the calibration of the assay. Upon the addition of the sample, the oxidative reactions initiated by the hydroxyl radicals present in the reaction mix are suppressed by the antioxidant components of the sample, preventing the colour change and thereby providing an effective measure of the total antioxidant capacity of the sample. Briefly, 30 µL serum and 500 µL reagent 1 (acetate buffer 0.4 mol/L, pH 5.8) were added to the test tube and stirred. 75 µL reagent 2 (acetate buffer 0.4 mol/L, and ABTS 30 mmol/L) was added to the mixture. The absorption of the solution at 660 nm was measured at 30 s (value A1) and 5 min (value A2) after mixing. The results are expressed as mmol Trolox equivalents/L for pleural fluid samples.

Ethical approval was obtained from Afyonkarahisar Health Sciences University, with the date and number 2019/04/05 and 2011-KAEK-2. A voluntary consent form was obtained from the patients. The study was carried out according to the ethical principles of the Declaration of Helsinki. This study was supported by Afyonkarahisar Health Sciences University's Scientific Research Projects Coordination Unit under the 19.TIP.012 grant number.

Statistical analysis

IBM (International Business Machines) SPSS (Statistical Package for the Social Sciences) v20 program was used for statistical analysis. G*POWER version 3.1.9.4 was used for power analysis. Power analysis was performed using the mean and standard deviation values obtained as a result of testing the quantitative data, and the power of the study was found to be 0.9511 under current conditions. As a result of the power analysis, 84 patients were included in the study. The conformity of quantitative data to the normal distribution was assessed using the Kolmogorov-Smirnov, Shapiro-Wilk, and graphical methods. Data were presented as mean ± standard deviation, number of subjects, and percentage. The Student's t-test was used if the two groups were normally distributed, and the Mann-Whitney U test was used if they did not fit the normal distribution. Receiver operating characteristic (ROC) curve analysis was performed to predict TAS, TOS, and PK cut-off values in transudate and exudate pleural fluid. The correlations among Light's parameters, PK, TAS, and TOS values were evaluated by the Pearson test. The Pearson chi-square or Fisher's exact test was used to compare qualitative data. A p-value of <0.05 was considered statistically significant.

Results

The majority of the 84 patients with PEs had parapneumonic effusion (n=23) and lung cancer (n=32). Four cases of malignant melanoma, three cases of small cell lung cancer, and 14 adenocarcinomas were found among patients with lung cancer. Twenty-one (50 %) of the 42 patients with transudative fluid were male, and 21 (50 %) were female. Seventeen (40.48 %) and 25 (59.52 %) of the 42 patients with exudative fluid were men, respectively. Patients with exudate and transudate fluid had similar sex ratios (p=0.124).

The correlation values of TAS, TOS, and PK were determined as r=0.328, p=0.002; r=0.406, p<0.001, and r=0.657, p<0.001, respectively. In this study, the age range of 84 patients containing 38 females (45.24 %) and 46 males (54.76 %) were between 20 and 90 years, and their mean age was 69.07 ± 13.29 years. The mean age of females was 68.13 years, and the mean age of males was 69.78. The mean ages of males and females were similar (p=0.211).

The age range of patients with transudative fluid was 26–90 years, with a mean age of 71.83 ± 12.79 years. The age range for patients with exudative fluid was 20–87 years, with a mean age of 66.31 ± 13.51 years. Transudate/exudate and mean age did not differ statistically significantly (p=0.056). Demographic characteristics are shown in Table 1.

There was no statistical difference between the serum biochemical test (glucose, albumin, protein, LDH, total cholesterol, triglyceride, and LDL-C) values of the transudate and exudate groups. There was a statistically significant difference in the groups' pleural fluid biochemical values for glucose, albumin, protein, LDH, total cholesterol, triglycerides, and LDL-C (p values, respectively: p=0.001, p<0.001, p<0.001, p<0.001, p<0.001, p=0.004, p<0.001). Protein and albumin gradients were similar (Table 2).

The two groups had differences in the mean values of TAS, TOS, and PK (Table 3).

The cut-off values for TAS, TOS, and PK in transudate-exudate separation were established as 13.54 mmol trolox equivalent/L, 13.88 µmol H_2O_2 equivalent/L, and 10.64 U/L, respectively, in the ROC (Receiver Operating Characteristics) analysis. The sensitivity and specificity values for TAS, TOS, and PK are presented in Table 4 and Figure 1.

As a result of the cytological examination of the pleural fluid of the patients, 23 malignant (7 transudates, 16 exudates) and 61 benign (35 transudates, 26 exudates) results were obtained. It was statistically significant (p=0.028).

TAS, TOS, and PK were not statistically significant in the differentiation of benign/malignant (p>0.05) in Table 5.

A non-specific culture examination of the patient's pleural fluid revealed that there was no growth in 81 (96.43 %) of the cases. All were discovered in exudative pleural fluid during a non-specific culture examination; 1

Table 1: Demographic characteristics.

Variables	Transudate	Exudate	Total	p-Value
Age, years[a]	71.83 ± 12.79	66.31 ± 13.51	69.07 ± 13.29	0.056
Gender, n (%)				
Female	21 (50 %)	17 (40.48 %)	38 (45.24 %)	
Male	21 (50 %)	25 (59.52 %)	46 (54.76 %)	
Total	42 (100 %)	42 (100 %)	84 (100 %)	0.124

[a]Age data are given as mean ± standard deviation.

Table 2: Serum and pleural fluid biochemical values of transudate and exudate groups.

	Serum fluid			Pleural fluid		
	Transudate	Exudate	p-Value	Transudate	Exudate	p-Value
Glucose, mg/dL	135.2 ± 52.4	123.5 ± 40.2	0.204	135.4 ± 47.9	102.8 ± 50.5	<0.001
Albumin, g/dL	3.34 ± 0.57	3.23 ± 0.78	0.761	1.88 ± 0.81	2.84 ± 0.85	<0.001
Protein, g/dL	6.53 ± 1.34	5.92 ± 1.42	0.161	2.88 ± 1.13	4.98 ± 1.20	<0.001
LDH, U/L	349.5 ± 161.1	318.1 ± 168.6	0.202	120.0 ± 45.0	744.0 ± 916	<0.001
Total cholesterol, mg/dL	168.0 ± 65.1	138.6 ± 57.5	0.372	56.4 ± 30.2	102.0 ± 53.3	<0.001
Triglyceride, mg/dL	122.6 ± 73.4	118.8 ± 61.5	0.961	46.2 ± 37.6	70.50 ± 45.8	0.004
LDL, mg/dL	116.4 ± 51.1	112.6 ± 49.3	0.728	24.7 ± 13.6	47.2 ± 20.7	<0.001
Albumin gradient, g/dL				1.45 ± 0.12	0.38 ± 0.13	0.064
Protein gradient, g/dL				3.64 ± 0.17	0.93 ± 0.25	0.057

Results are given means ± standard deviations. LDH, lactate dehydrogenase; LDL, low-density lipoprotein.

Table 3: TAS, TOS and PK values in pleural fluid.

Pleural fluid	Total	Transudate	Exudate	p-Value
TAS, mmol Trolox Eq/L	15.08 ± 4.16	13.72 ± 2.71	16.45 ± 4.89	0.027
TOS, µmol H_2O_2 Eq/L	15.34 ± 5.01	13.32 ± 3.13	17.36 ± 5.71	0.002
PK, U/L	12.44 ± 4.86	9.26 ± 1.98	15.62 ± 4.82	0.001

TAS, total antioxidant status; TOS, total oxidant status; PK, pyruvate kinase.

(1.19 %) each of *Acinetobacter baumannii*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa*. In any pleural fluids, *Mycobacterium tuberculosis* bacillus could not be found by ARB staining, and mycobacteria did not grow in the culture.

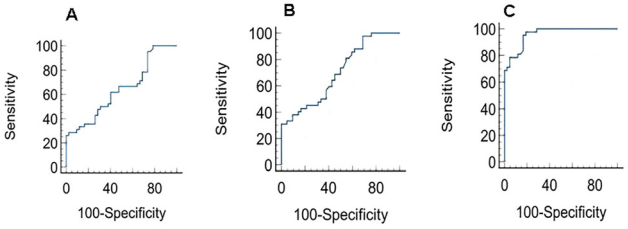

Figure 1: Receiver-operating characteristics (ROC) curves for total antioxidant status (TAS) (A), total oxidant status (TOS) (B), pyruvate kinase (PK) (C).

Table 5: Relationship between TAS TOS and Pyruvate Kinase in benign and malignant cytology.

Pleural liquid	Cytology		
	Benign	Malign	p-Value
TAS[a], mmol Trolox Eq/L	15.26 ± 420	14.62 ± 4.09	0.988
TOS[a], µmol H_2O_2 Eq/L	15.46 ± 4.93	15.03 ± 5.29	0.743
PK [a], U/L	11.85 ± 4.84	14.00 ± 4.68	0.071

PK, pyruvate kinase; TOS, total oksidant status; TAS, total antioxidant status.
[a]Data are given as means ± standard deviations.

Discussion

Pleural effusion is a common condition that clinicians have difficulty diagnosing and treating. Transudative and exudative PE must be distinguished first in patients with PE. Although Light's criteria are used internationally to distinguish transudate and exudate, the differentiation between transudate and exudate pleural fluid is still unclear in some cases [15]. In this study, we assessed the diagnostic utility of especially PK values and oxidative stress parameters in transudate-exudate differentiation in pleural liquids due to the necessity for alternative distinguishing indicators and/or biomarkers. We have demonstrated that the levels of PK, TAS, and TOS were statistically significantly higher in the exudative fluid. Additionally, in the differentiation of benign

Table 4: Cut-off, sensitivity, and specificity values for TAS, TOS, and PK in the differentiation of transudate-exudate by ROC analysis.

Variables	AUC(95 % CI)	Cut-off	p-Value	Sensitivity, %	Specificity, %
TAS, mmol Trolox Eq/L	0.640 (0.528–0.742)	13.54	0.021	66.67	52.38
TOS, µmol H_2O_2 Eq/L	0.699 (0.589–0.794)	13.88	0.002	64.29	57.14
PK, U/L	0.958 (0.891–0.999)	10.64	0.001	97.62	80.95

ROC, receiver operating characteristics; AUC, area under the ROC curve; CI, confidence interval; TAS, total antioxidant status; TOS, total oxidant status; PK, pyruvate kinase.

and malignant pleural fluid, oxidative stress parameters and PK levels were not statistically significant.

Free radicals and reactive oxygen species (ROS) that are generated in metabolic and physiological processes may be harmful to cellular components like nucleotides, proteins, and lipids [16, 17]. ROS are removed via enzymatic and nonenzymatic antioxidative mechanisms. While oxidant molecules such as ROS increase in various pathological conditions, the effectiveness of antioxidant defense systems decreases. TOS and TAS are oxidative stress parameters that are widely used to demonstrate the oxidative balance in organisms [17–20]. It is known that oxidative stress increases in lung diseases [21, 22]. A few studies have investigated the role of oxidative stress parameters in the differential diagnosis of transudative and exudative PE. They may be useful for the differentiation of transudate and exudate pleural fluid [23]. The study of Iclal et al. reported that pleural TAS value was significantly higher in exudate groups but not significant in TOS values according to the comparison of the transudate and exudate groups containing 14 and 47 people, respectively. Their ROC analysis showed that the cut-off value of pleural TAS was 0.87 (AUC: 0.794, sensitivity: 74 %, and specificity: 70 %) [24]. Similar to this study, we also found that TAS levels were significantly higher in the exudate group. However, we reported that TOS was significantly higher in exudative pleural fluid, contrary to the study of Iclal et al. In our study, the levels of TOS (AUC: 0.699, sensitivity: 64.29 % and specificity: 57.14 %) and TAS (AUC: 0.640, sensitivity: 66.67 % and specificity: 52.38 %) in the ROC analysis were not found as sensitive and specific as Light's criteria in the differentiation of transudate and exudate in the pleural fluids. Therefore, TAS and TOS analysis only points out the presence of oxidative stress and antioxidant capacity. Although this non-specific analysis can not be used as diagnostic markers in any pathological condition, they may be tools for observing the response to the therapy.

PK catalyzes the transfer of a phosphate group from phosphoenolpyruvate (PEP) to adenosine diphosphate (ADP), yielding pyruvate and ATP. PK is one of the most critical enzymes for the control of metabolic pathways following glycolysis since, as an irreversible product of the reaction catalyzed by PK, pyruvate is used in various metabolic pathways [25, 26]. Different isoenzymes of pyruvate kinase are expressed depending on the metabolic responsibilities of the various cells and tissues [9]. Pyruvate kinase L is a PK isoenzyme specifically found in tissues such as the liver and kidney, where gluconeogenesis reactions occur. Erythrocytes express pyruvate kinase R of PK isoenzymes. Pyruvate kinase M1 is located in tissues where large amounts of energy have to be rapidly provided, such as in muscles and the brain. Lung tissues and all cells with high rates of nucleic acid production, including all proliferating cells, including embryonic cells, adult stem cells, and particularly tumor cells, are characterized by the presence of pyruvate kinase M2 (PKM2) [27, 28]. Zhang T. et al. reported that the differential cut-off value, sensitivity, and specificity were 28.67 U/mL (AUC: 0.856), 68.8 %, and 52.5 %, respectively, when they compared the diagnostic value of PKM2 in the benign and malignant PE groups with 85 and 125 subjects, respectively [29]. In another study with 34 lung cancer patients and 34 controls, Elia S. et al. reported that PKM2 was significantly higher in lung cancer with the cut-off value and sensitivity of PKM2 (32.9 U/mL and 85.7 % respectively), and they suggested that PKM2 could be used as a marker to distinguish between malignant and benign PE [30]. However, to our knowledge, PK has not been tested in distinguishing between transudate and exudate in Pleural Liquids. The total activities of PK enzymes were analyzed, but PKM2 of PK isoenzymes was not analyzed as a limitation of the study. Therefore, we concluded that the difference in the pleural fluid between benign and malignant was not statistically significant ($p>0.05$).

Although Light's criteria have been the accepted standard for distinguishing between transudates and exudates for several years, there are still some concerns with the misclassifications. Recently, some measurements have been made to differentiate between transudative PEs and exudative PEs. Hamm et al. reported significantly increased cholesterol levels in exudative pleural fluid [31]. Moreover, Garcia-Pachon investigated cholinesterase levels to differentiate between transudative and exudative pleural in pleural fluid [32]. In a study similar to our study concept in recent years, a significant increase in CRP level was found in the exudate group. The study demonstrated that the cut-off, sensitivity, and specificity values were determined as 3.31 mg/dL, 96.3 %, and 72.1 %, respectively, and they recommended that the level of CRP in the effusion fluid could help differentiate exudative from transudative PEs [33]. In our study, it was determined that the cut-off, sensitivity, and specificity values of PK were 10.64 U/L, 97.62 %, and 80.95 %. We have suggested that PK level can be useful in the distinction between transudate and exudate in addition to the Light's criteria.

Conclusions

This study established that there is no significant difference between malignant and benign PEs based on the usage of PK, TAS, and TOS. We believe that PK can be employed to distinguish between transudate and exudate in PE patients in addition to Light's criteria.

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Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: The study was performed under a protocol approved by the Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (2019/6/155).

References

1. Abou-Zeid SM, AbuBakr HO, Mohamed MA, El-Bahrawy A. Ameliorative effect of pumpkin seed oil against emamectin induced toxicity in mice. Biomed Pharmacother 2018;98:242–51.
2. Broaddus VC, Light RW. What is the origin of pleural transudates and exudates? Chest 1992;102:658–9.
3. He T, Oh S. Diagnostic approach to pleural effusions. AME Med J 2018;3: 1–9.
4. Vives M, Porcel JM, de Vera MV, Ribelles E, Rubio M. A study of Light's criteria and possible modifications for distinguishing exudative from transudative pleural effusions. Chest 1996;109:1503–7.
5. Rufino R, Marques BL, de Lima Azambuja R, Mafort T, Pugliese JG, da Costa CH. Pleural cholesterol to the diagnosis of exudative effusion. Open Respir Med J 2014;8:14.
6. Uslu Ö, Tuksavul F, Kabakoğlu NI, Gülpek M, Kazancı M, Güçlü SZ. Plevral sıvılarda transuda-eksuda ayrımında yeni biyokimyasal formüllerin tanısal verimliliği. Toraks Dergisi 2006;7:34–9.
7. José MP. Identifying transudates misclassified by Light's criteria. Curr Opin Pulm Med 2013;19:362–7.
8. Soliano JS, Jorge MC. Comparing pleural fluid cholesterol and lactate dehydrogenase (Costa S. criteria) and Light S. criteria in separating exudates from transudates. Chest 2008;134:57.
9. Israelsen WJ, Vander Heiden MG, editors. Pyruvate kinase: function, regulation and role in cancer. Semin Cell Dev Biol 2015;43:43–51.
10. Al-Samkari H, Van Beers EJ, Kuo KH, Barcellini W, Bianchi P, Glenthøj A, et al. The variable manifestations of disease in pyruvate kinase deficiency and their management. Haematol 2020;105:2229.
11. Yumru M, Savas HA, Kalenderoglu A, Bulut M, Celik H, Erel O. Oxidative imbalance in bipolar disorder subtypes: a comparative study. Prog Neuro-Psychopharmacol Biol Psychiatry 2009;33:1070–4.
12. Mercer RM, Corcoran JP, Porcel JM, Rahman NM, Psallidas I. Interpreting pleural fluid results. Clin Med 2019;19:213.
13. Erel O. A new automated colorimetric method for measuring total oxidant status. Clin Biochem 2005;38:1103–11.
14. Erel O. A novel automated method to measure total antioxidant response against potent free radical reactions. Clin Biochem 2004;37:112–9.
15. Jany B, Welte T. Pleural effusion in adults—etiology, diagnosis, and treatment. Dtsch Arztebl Int 2019;116:377.
16. Ozcan M, Esendagli G, Musdal Y, Canpinar H, Bacanlı M, Anlar HG, et al. Dual actions of the antioxidant chlorophyllin, a glutathione transferase P1-1 inhibitor, in tumorigenesis and tumor progression. J Cell Biochem 2019;120:7045–55.
17. Rao PS, Kalva S, Yerramilli A, Mamidi S. Free radicals and tissue damage: role of antioxidants. Free Radic Antioxidants 2011;1:2–7.
18. Ceylan S, Harsit B, Saral O, Ozcan M, Sonmez E. Investigation of antioxidant and antimicrobial activities of medicinal plants grown in the eastern black sea region of Turkey. Med Sci Discov 2018;5: 245–52.
19. Karuppanapandian T, Moon J-C, Kim C, Manoharan K, Kim W. Reactive oxygen species in plants: their generation, signal transduction, and scavenging mechanisms. Aust J Crop Sci 2011;5:709–25.
20. Ozcan M, Aydemir D, Bacanlı M, Anlar HG, Ulusu NN, Aksoy Y. Protective effects of antioxidant chlorophyllin in chemically induced breast cancer model in vivo. Biol Trace Elem Res 2021;199:4475–88.
21. Ciencewicki J, Trivedi S, Kleeberger SR. Oxidants and the pathogenesis of lung diseases. Allergy Clin Immunol 2008;122:456–68.
22. Rahman I. Oxidative stress in pathogenesis of chronic obstructive pulmonary disease. Cell Biochem Biophys 2005;43:167–88.
23. Papageorgiou E, Kostikas K, Kiropoulos T, Karetsi E, Mpatavanis G, Gourgoulianis KI. Increased oxidative stress in exudative pleural effusions: a new marker for the differentiation between exudates and transudates? Chest 2005;128:3291–7.
24. Hocanli I, Koyuncu I. Oxidative stress parameters as biomarkers for differentiating exudate and transudate pleural fluid. Clin Lab 2022;68: 3.
25. Ercan M, Canikliogluu A, Oguz EF, Yucel C, Ozcan M, Yilmaz FM, et al. The effect of measurement uncertainty for HOMA-IR in assessment of insulin resistance. Med Sci 2019;8:32–6.
26. Gray LR, Tompkins SC, Taylor EB. Regulation of pyruvate metabolism and human disease. Cell Mol Life Sci 2014;71:2577–604.
27. Yamada K, Noguchı T. Nutrient and hormonal regulation of pyruvate kinase gene expression. Biochem J 1999;337:1–11.
28. Mazurek S, Boschek CB, Hugo F, Eigenbrodt E, editors. Pyruvate kinase type M2 and its role in tumor growth and spreading. Semin Cancer Biol 2005;15:300–8.
29. Zhang T, Liu W, Li L, Jue Z, Xu C. Evaluation of serum and pleural levels tumor M2-pyruvate kinase in lung cancer patients with pleural effusion. BMC Pulm Med 2022;22:307.
30. Elia S, Massoud R, Guggino G, Cristino B, Cortese C, De Massimi AR, et al. Tumor type M2-pyruvate-kinase levels in pleural fluid versus plasma in cancer patients: a further tool to define the need for invasive procedures. Eur J Cardio Thorac Surg 2008;33: 723–7.
31. Hamm H, Brohan U, Bohmer R, Missmahl H-P. Cholesterol in pleural effusions: a diagnostic aid. Chest 1987;92:296–302.
32. Garcia-Pachon E, Padilla-Navas I, Sanchez JF, Jimenez B, Custardoy J. Pleural fluid to serum cholinesterase ratio for the separation of transudates and exudates. Chest 1996;110:97–101.
33. Rismantab O, Moosavi SAJ, Farahnak MR, Dastoorpoor M, Raji H. Role of CRP as a marker for discrimination of exudative and transudative pleural effusion. Monaldi Arch Chest Dis 2022;92:2059.