RESEARCH

Comparison of Laboratory Results and Chest Computed Tomography Scans of COVID-19 Patients: A Pilot Study

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Abstract: In this article, we aimed to investigate lung involvement in patients suffering from the new Coronavirus Disease 2019 (COVID-19) and to determine laboratory markers that indicate lung involvement. Patients diagnosed with COVID-19 pneumonia were included 90 patient in Group 1, while Group 2 comprised 60 patients in the control group and total of 150 patient. CCT scans of the study patients were transferred to the Intrasense Myrian® software (Myrian; Intrasense, Montpellier, France) and 3D models of the data were generated. Mean levels of D-dimer, fibrinogen and C-reactive protein (CRP) in Group 1 were 515±958 µg/L, 467±182 mg/dL and 5.67±5.46 mg/dL, respectively, whereas those in Group 2 were 129±120 µg/L, 345±113 mg/dL and 1.32±2.58 mg/dL, respectively (P<0.001). Right lung volume (RLV), left lung volume (LLV) and total lung volume (TLV) of Group 1 patients were 2419±554 cm^3, 1857±634 cm^3 and 3929±1297 cm^3, respectively, while those measurements in Group 2 were 2483±503 cm^3, 2118±535 cm^3 and 4538±1079 cm^3, respectively (P<0.001). Reduction of total lung volumes correlates with increase in levels of D-dimer and CRP and decrease in lymphocyte counts. Lung volumes of patients who develop Covid-19 pneumonia decrease. D-dimer, CRP and fibrinogen levels increase and lymphocyte levels decrease in these patients.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first reported in December 2019 in the city of Wuhan, China[1]. After COVID-19 spread outside China to a number of countries, it was declared a public health emergency. Eventually, the World Health Organization (WHO) announced that COVID-19 is a pandemic[2]. COVID-19 is highly infectious and can cause severe pneumonia. In severe cases, the disease may progress rapidly, and lead to acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, coagulation dysfunction, acute cardiac injury, acute kidney injury and death[3]. The most common symptoms in COVID-19 patients are fever, cough and shortness of breath. Routine laboratory tests indicate lymphopenia, and high levels of D-dimer, C-reactive protein (CRP) and procalcitonin[3,4]. There is an urgent need for early and effective predictors of clinical outcomes for risk stratification of Covid-19 patients. D-dimer results from the formation and breakdown of cross-linked fibrin and reflects the activation of coagulation and fibrinolysis. It has been reported that Covid-19 is associated with hemostatic abnormalities and significantly higher D-dimer levels were observed in non -survivors[5]. Degree of D-dimer elevation positively correlates with mortality in COVID-19 patients. COVID-19 also leads to arterial thrombotic events (including strokes and ischemic limbs) as well as microvascular thrombotic disorders (as frequently documented at autopsy in the pulmonary vascular beds)[6]. Also, the CRP marker was found to be significantly increased in the initial phases of the infection for severe COVID-19 patients, also prior to indications of critical findings with CT. Importantly, CRP has been associated with disease development and is an early predictor for severe COVID-19[7].

Nonetheless, clinical findings and routine laboratory tests are nonspecific in COVID-19 pneumonia. Currently, the standard diagnosis method for COVID-19 is detection of viral nucleic acid with real-time reverse polymerase chain reaction (RT-PCR)[3,4]. However, waiting period for RT-PCR results may lead to delayed diagnosis of COVID-19 pneumonia. Moreover, RT-PCR can produce negative results during the initial phase of COVID-19 pneumonia[4].

Accordingly, chest X-ray and computed tomography (CT) scans of patients with suspected COVID-19 pneumonia are frequently performed. In literature, the diagnostic value of chest x-ray is relatively low as 30–60% in COVID-19 pneumonia. Still, some anomalies can be observed on chest

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radiographs of viral pneumonia cases[4]. If COVID-19 cannot be ruled out in patients with normal chest radiography, non-contrast chest computed tomography (CCT) scans are used for early diagnosis of suspected viral disease[4,8].

In various diseases, volumes of organs and/or masses are measured using computer software. Measurement of lung volume is similarly carried out[9-12]. The most common patterns on CCT scans of COVID-19 patients are ground-glass opacity (GGO), interlobular septal thickening, bilateral irregular consolidations and air bronchograms. In addition to these patterns, quantitative analysis of lung has revealed volume loss in effected lobes[13-15].

Even though CT imaging is very useful for early diagnosis, the absorbed radiation dose is high and recurring scans lead to elevated radiation exposure. Consequently, medical doctors have to make difficult decisions when ordering CT scans, especially for certain patients such as children and pregnant women, and when imaging needs to be repeated. In this regard, research has been done comparing laboratory parameters and CT findings. Such studies have investigated the relation between the severity of pneumonia findings on CT scans and biochemical parameters[16,17]. However, the literature does not include a comparison of laboratory results of patients with and without pneumonia.

The aims of this study are to investigate lung involvement in patients infected with the COVID-19 virus and to establish laboratory markers that indicate lung involvement in these patients.

MATERIALS and METHODS

This retrospective study was conducted after the approval of Alaaddin Keykubat University Faculty of Medicine Ethics Committee (2020, 18-16). Among patients that visited the emergency department between 30.03.2020 and 31.08.2020 with complaints of cough, fever and short of breath, those that underwent CCT, were diagnosed with COVID-19 pneumonia, and were aged 18 or older were included in the study. Diagnoses of COVID-19 were verified with RT-PCR from nasopharyngeal swap samples. The control group was formed from cardiovascular surgery outpatients that underwent CCT for any reason, whose CCT scans were evaluated as normal. Patients diagnosed with COVID-19 pneumonia were placed in Group 1, while Group 2 constituted of patients from the control group with negative COVID-19. Patients with chronic respiratory diseases such as asthma and bronchitis were not included in the study. Patient information was collected from the hospital automation system and their inpatient files. Evaluation of the study patients' CCT scans was based on the official reports on the hospital automation system. Patients without CCT scans or whose scans were taken at another facility, patients whose CCT scans indicated findings other than viral pneumonia (cyst, mass, edema, bacterial pneumonia, pneumothorax, hydrothorax, pleural effusion, pericardial effusion, aorta aneurism, etc.), those younger than 18, and those with unavailable information were excluded from the study. A standard data collection form was prepared, on which patients' file number, age, gender, laboratory results, CCT report, place of admission and clinical outcomes were recorded.

Biochemical Analysis

D-dimer levels were measured with an ACL TOP 500 device (Instrumentation Laboratory, Munich, Germany). CRP levels were measured with an Abbott Architect C800. Hemogram was studied with a Sysmex XN100. The reference values reported in healthy adults were as follows: 0-0.5 mg/dL for CRP, 0-240µg/dL for D-dimer and 1.26-3.35 x 103 cells/µL for lymphocyte.

Chest Computed Tomography Imaging

Chest Computed Tomography scans were obtained from the hospital automation system. A multislice computed tomography scanner (TOSHIBA Alexion 16 slice) was used for CCT imaging at the emergency department. CCT scans of COVID-19 cases were transferred to the Intrasense Myrian Software (Myrian; Intrasense, Montpellier, France) and 3D models of the images were re-created. This process generates 3D images by identifying anatomical structures of the patient and coloring the area of interest. In this study, lung areas were designated on the CCT images transferred to the Myrian software and these areas were colored afterwards. Right lung volumes (RLV) and left lung volumes (LLV) were measured, which were added up to find the total lung volume (TLV). These measurements were carried out by an anatomy specialist. All data were recorded on the data collection form.

Statistical analysis

IBM SPSS Statistics version 21.0 software package was used for statistical analysis of the data gathered in the study. For determining whether the distribution of continuous and discontinuous quantitative variables was normal, skewness-curtosis, std/MEAN, histogram, Q-Q plot and Kolmogorov-Smirnov test was utilized. For normal normally distributed data descriptive statistics were given as mean ± standard deviation. While, non-normally distributed datas was shown median (minimum-maximum) for continuous and discontinuous quantitative variables, and as number of cases (percentage) for categorical variables. Categorical variables were analyzed with the Pearson Chi-squared test, parametric data with the Student's t-test, and non-parametric data with the Mann-Whitney U for comparison of two independent variables. Assessment of correlation was made using the Spearman Rho's correlation analysis for data with non parametric distribution. Using receiver operating characteristics (ROC) analysis, the cut-off value fitting the are under the curve (AUC), specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) were calculated.

RESULTS

A total of 150 patients were included in the study, 90 of which in Group 1 and 60 in Group 2. The mean age in Group 1 was 55±18 years, while that in Group 2 was 50±15 years (p=0.092). Group 1 consisted of 61 (54%) males and 29 (46%) females, whereas Group 2 included 31 (56%) males and 29 (44%) females (p=0.060). There was no significant difference between Group 1 and 2 patients in terms of past medical history (Table 1).

Table 1. Chronic Diseases of Patients' History by Pearson Chi-Square

Disease	Group 1	Group 2	p
Diabetus Mellitus	18	10	0.673
Hypertension	25	11	0.242
Coronary Artery Disease	17	9	0.661
Chronic Obstructive Pulmonary Disease	8	10	0.200

There is no difference in the frequency analysis of chronic diseases by groups (p>0.05).

Laboratory results and lung volumes exhibited differences between patients in Group 1 and Group 2. Levels of D-dimer, CRP, fibrinogen and neutrophils were higher in Group 1 patients compared to those in Group 2 patients. White blood cell (WBC), lymphocyte, eosinophil, basophil and platelet counts were lower in Group 1 than those in Group 2. When lung volumes were compared, RLV, LLV and TLV in Group 1 patients were found to be lower compared to those in Group 2 (Table 2, 3; Figure 1,2).

Table 2. Comparison of the laboratory results of the groups by Mann-Whitney U Test

Laboratory results	Group	Median	Min-Max	p
D-Dimer (µg/L)	Group 1***	260	34-6450	0.001
	Group 2	103	3-767	
C-reactive protein (mg/dl)	Group 1***	3.7	0.1-22	0.001
	Group 2	0.20	0.1-19	
Fibrinogen	Group 1	313	193-686	0.001
	Group 2***	455	85-1037	
White blood cell (10^3/µL)	Group 1	6.07	2.60-24.93	0.005
	Group 2**	7.41	3.22-14.89	
Neutrophil (10^3/µL)	Group 1*	4.93	1.71-18.65	0.028
	Group 2	4.25	0.63-31.87	
Lymphocyte (10^3/µL)	Group 1	1.52	0.21-8.07	0.001
	Group 2***	2.35	0.92-5.42	
Eosinophil (10^3/µL)	Group 1	0.02	0.00-1.00	0.001
	Group 2***	0.14	0.00-1.01	
Basophil (10^3/µL)	Group 1	0.02	0.00-0.12	0.001
	Group 2**	0.04	0.02-0.61	
Platelet (10^3/µL)	Group 1	202	106-535	0.037
	Group 2*	243	69-523	

*The difference is statistically significant (p<0.05)
** The difference is statistically significant (p<0.01)
*** The difference is statistically significant (p<0.001)

Table 3. Comparison of the lung volumes of the groups by Independent Samples T-Test

	Groups	Mean± SD	p
Total Lung volume (cm^3)	Group 1	3929±1297	0.002
	Group 2**	4538±1079	
Right Lung Volume (cm^3)	Group 1	2419±554	0.005
	Group 2**	2483±503	
Left Lung Volume	Group 1	1857±634	0.008
	Group 2**	2118±535	

*The difference is statistically significant (p<0.05)
** The difference is statistically significant (p<0.01)

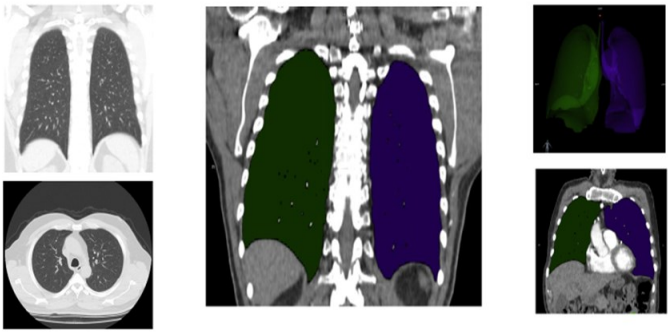

Figure 1. A 48-year-old male patient was admitted to the cardiovascular surgery outpatient clinic with a complaint of chest pain. The laboratory results of the patient were D-dimer: 34 µg/L, CRP: 5.30 mg/dl, Lymphocyte: 3.34 10^3/µL. Lung volumes of the patient were measured as Right lung: 3069 cm^3, Left lung: 2527 cm^3, Total lung: 5596 cm^3, respectively.

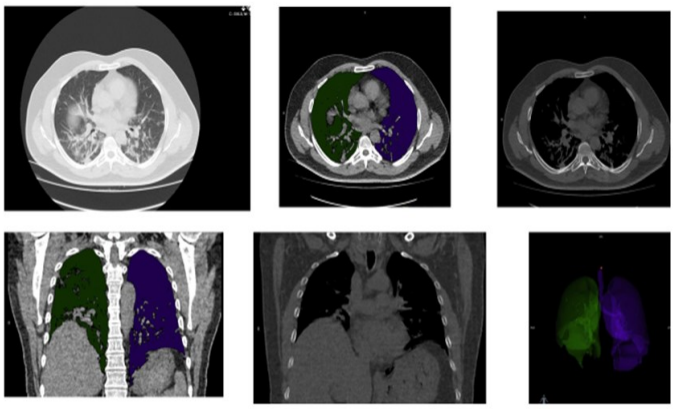

Figure 2. 54-year-old male patient was admitted to the emergency department with fever and shortness of breath. The laboratory results of the patient were D-dimer: 542 µg/L, CRP: 12.70 mg/dl, Lymphocyte: 2.19 10^3 / µL. Lung volumes of the patient were measured as Right lung:1392 cm^3, Left lung: 1519 cm^3, Total lung: 2911 cm^3 respectively. The patient was hospitalized in the intensive care unit.

Correlation analysis between lung volumes and laboratory results of all patients revealed a negative correlation between D-dimer levels and TLV. CRP levels negatively correlated with RLV, LLV and TLV. There was a positive correlation between lymphocyte count and TLV (Table 4).

ROC analysis was performed in order to determine which laboratory parameters could be used as markers for the presence of pneumonia on CT scans. AUC of CRP, D-dimer and fibrinogen were the highest, in decreasing order. AUC of WBC, lymphocyte, neutrophil, basophil and eosinophil counts were notably low.

When the cut-off value for D-dimer was set at 260 µg/L, sensitivity was 50%, specificity was 88%, PPV was 87% and NPV was 49%. Sensitivity, specificity, PPV and NPV for CRP were calculated as 48%, 90%, 88% and 53%, respectively, when the cut-off value was 4.2 mg/dL. With a cut-off value of 459 mg/dL for fibrinogen, sensitivity, specificity, PPV and NPV were 50%, 82%, 80% and 47%, respectively. (Table 5; Figure 3).

Eighteen Group 1 patients were admitted to the intensive care unit and 72 were admitted to hospital wards.

DISCUSSION

Due to the lack of preventive immunity in humans, the SARS-CoV-2 virus can proliferate in infected tissues. Subsequent cell death, and release of viral particles and cellular components into the intercellular space lead to activation of the inflammatory response. Studies have shown that increase in inflammation indicators CRP, D-dimer and erythrocyte sedimentation rate (ESR), as well as lymphopenia develop during the course of the disease, and that these parameters are related to the severity of the disease[3,18,19].

As recent studies have reported, in addition to inflammation, COVID-19 is usually associated with coagulopathy and the major cause of death is disseminated intravascular coagulation. It has been shown that abnormal coagulation artifacts, especially D-dimer and fibrin degradation products, are significantly elevated in deceased cases[20-22]. Adding to the increasing number of reports of high D-dimer levels, gradual rise in D-dimer levels during the course of the disease has been found to be associated worsening of the disease[18,23,24].

Studies that examined CT scans of COVID-19 patients have shown that disease progression correlated with increase in number, density and size of GGO. Another study has reported that depending on the severity of the disease, the number of effected lung segments and lobes, and incidence of consolidation, crazy-paving pattern and air bronchograms were elevated in more severe cases[25]. Furthermore, patients with normal early-phase CT scans exhibited bilateral GGO on their control CT scans taken 3-4 days later. On the other hand, disease progression was not severe in patients without X-ray or CT findings[3,13,14]. Additionally, various studies have been conducted that

Table 4. Spearman Rho's Correlation Between Patients' Lung Volumes and Laboratory Levels

Laboratory results	Correlation	Right Lung Volume	Left Lung Volume	Total Lung Volume
D-dimer	R	-0.124	-0.153	-0.173
	P	0.130	0.061	0.034
C-Reactive protein	R[a]	-0.187*	-0.186	-0.208
	P	0.022	0.023	0.011
Fibrinogen	R	-0.051	-0.060	-0.064
	P	0.533	0.467	0.434
White blood cell	R	0.024	0.018	0.047
	P	0.771	0.827	0.568
Neutrophil	R	-0.069	-0.068	-0.046
	P	0.404	0.409	0.576
Lymphocyte	R	0.139	0.124	0.163
	P	0.089	0.130	0.046
Basophil	R	-0.043	-0.004	-0.017
	P	0.605	0.966	0.838
Eosinophil	R[a]	0.163*	0.160	0.153
	P	0.046	0.050	0.062

R: corellation coefficent
a; 0<r<0.30 Very week correlation between volume and serum parameters

Table 5. ROC analysis of laboratory levels to be used as markers in Covid-19 pneumonia

Laboratory Test Results	AUC	Asymptotic 95% Confidence Interval	
		Lower Bound	Upper Bound
D-dimer	0.794	0.723	0.864
C- reactive protein	0.835	0.767	0.904
Fibrinogen	0.718	0.635	0.800
White blood cell	0.365	0.275	0.454
Lymphocyte	0.235	0,157	0.312
Neutrophil	0.394	0.304	0.485
Basophil	0.201	0.130	0.272
Eosinophil	0.240	0.161	0.318
Platelet	0.395	0.302	0.488

AUC: Area Under the Curve

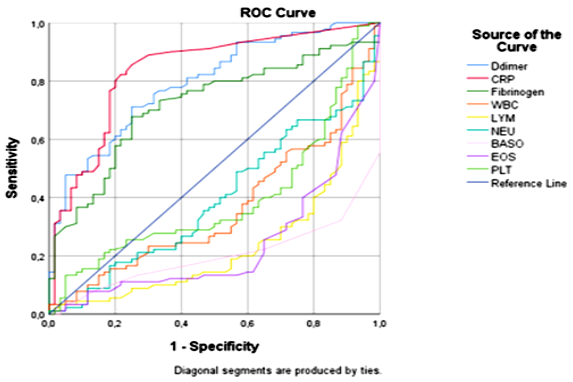

Figure 3. Receiver Operating Characteristic (ROC) Curve for D-Dimer, CRP and Lymphocyte in Covid-19 Pneumonia

investigated the relation between CT findings and markers of inflammation, as well as coagulation. Such research has indicated that as CT findings worsened, CRP levels, ESR and granulocyte/ lymphocyte ratio increased, whereas lymphocyte counts decreased. In another study, ROC analyses of CRP and ESR have been used to determine the severity of COVID-19 at the time of patients' first visit. This study reported AUC of CRP and ESR as 0.87 and 0.78, respectively. For a cut-off value of 20.42 mg/L for CRP, sensitivity, specificity, PPV and NPV were 83%, 91%, 71% and 95%, respectively[16,17].

Our study showed that levels of D-dimer, CRP, fibrinogen and neutrophil increased, whereas WBC, lymphocyte, eosinophil, basophil and platelet counts decreased in patients that developed COVID-19 pneumonia. These findings are significant as they indicate that several parameters can potentially be used as markers for detecting pneumonia on CT scans.

In addition to examination of patterns on CT scans of COVID-19 patients, computer software has been recently used for estimating lung capacity. It has been established that such measurements are reliable and accurate for assessing severity and dispersion of pneumonia. In one study, volumes of total lung, right lung and lower right lobe were found to be lower in patients with severe disease compared to those with mild disease. This study has also shown that volumes of lesions were higher in severe cases[26]. Another paper has reported crazy-paving pattern on enlarged multiplanar reconstruction in all cases examined. The lobules with lesions were found to be 1 cm smaller than adjacent lobules. The same paper has also noted decrease in lung capacity in patients that required oxygen support[15].

In our study, right, left and total lung volumes were measured in both patient groups, which showed that RLV, LLV and TLV were reduced in patients that developed COVID-19 pneumonia. These findings are in agreement with results from previous studies. Additionally, our study included assessment of correlation between lung volumes and laboratory results in order to determine the cause of said reduction in lung volumes. There was strong negative correlation between TLV and levels of D-dimer and CRP, whereas TLV positively correlated with lymphocyte count. These results suggest that coagulopathy, in addition to inflammation, has an important role in reduction of lung volumes.

D-dimer levels are known to increase during thromboembolic events, such as acute pulmonary embolism (APE) and deep vein thrombosis. NPV of D-dimer is high in APE cases and a negative D-dimer test rules out APE[27]. Similar to pulmonary embolism, coagulopathy develops in COVID-19 together with inflammation. On the basis of these observations, we investigated the laboratory results that correspond to presence of pneumonia on CT scans. ROC analysis made accordingly revealed that AUC of CRP, D-dimer and fibrinogen levels were the highest, in decreasing order. AUC of WBC, lymphocyte, neutrophil, basophil and eosinophil counts were notably low. Furthermore, distinct from other studies, we determined cut-off values for D-dimer, fibrinogen and CRP. Using a cut-off value of 260 µg/L for D-dimer, sensitivity, specificity, PPV and NPV were calculated as 50%, 88%, 87% and 49%, respectively. When the cut-off value was set as 4.2 mg/dL for CRP, sensitivity was 48%, specificity was 90%, PPV was 88% and NPV was 53%. A cut-off value of 459 mg/dL for fibrinogen generated sensitivity, specificity, PPV and NPV of 50%, 82%, 80% and 47%, respectively. Although sensitivity and NPV of D-dimer, CRP and fibrinogen were low, these parameters were considered as potential markers for COVID-19 pneumonia, since their specificity and PPV were high.

In conclusion, reduction of lung volumes correlates with increase in levels of D-dimer and CRP and decrease in lymphocyte counts.

Lung volumes of patients who develop Covid-19 pneumonia decrease. D-dimer, CRP and fibrinogen levels increase and lymphocyte levels decrease in these patients. Consequently, levels of CRP, D-dimer and fibrinogen, as well as lymphocyte counts can be used as markers for diagnosis of COVID-19 pneumonia and exclusion of pneumonia and determining disease severity.

Limitations

In our study, laboratory parameters used in emergency cases were compared with CT scans. Broader laboratory analyses could not be performed due to insufficient data, which is the limiting factor of this study.

Conflict of interest

The authors have no conflict of interest to declare regarding the materials or methods used in this study or the findings presented in this paper.

Acknowledgements

M.E, N.K and S.A. contributed to study concept and design. M.E. and S.A. contributed to acquisition of the data. M.E, N.K and S.A. contributed to analysis and interpretation of the data. M.E, N.K and S.A. contributed to drafting of the manuscript and contributed to critical revision of the manuscript for important intellectual content. N.K. contributed to statistical expertise.

Ethical approval

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This retrospective study was conducted after the approval of Alanya Alaaddin Keykubat University Faculty of Medicine Ethics Committee (2020/18-13).

Informed consent

Our study was conducted retrospectively.

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REFERENCES

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5 PMID: 31986264.
2. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720. doi: 10.1056/NEJMoa2002032.
3. Xu G, Yang Y, Du Y, et al. Clinical pathway for early diagnosis of COVID-19: updates from experience to evidence-based practice. *Clin Rev Allergy Immunol.* 2020;24; 1-12. doi: 10.1007/s12016-020-08792-8. PMID: 32328954.
4. Akcay S, Ozlu T, Yilmaz A. Radiological approaches to COVID-19 pneumonia. *Turk J Med Sci.* 2020;50(SI-1):604-610. doi:10.3906/sag-2004-160.
5. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. *J Thromb Haemost* 2020; (6):1324-1329. doi: 10.1111/jth.14859.
6. Wool D.G, Miller J.L. The Impact of COVID-19 disease on platelets and coagulation. *Pathobiology*. 2021;88(1):15-27. doi: 10.1159/000512007. Epub 2020 Oct 13.
7. Pontia G, Maccaferrib M, Ruinia C, et al. Biomarkers associated with COVID-19 disease progression. *Crit Rev Clin Lab Sci.* 2020;57(6):389-399. doi: 10.1080/10408363.2020.1770685. Epub 2020 Jun 5.
8. Meng H, Xiong R, He R, et al. CT imaging and clinical course of asymptomatic cases with COVID-19 pneumonia at admission in Wuhan, China. *J Infect.* 2020;81(1):e33-e39. doi: 10.1016/j.jinf.2020.04.004. PMID: 32294504.
9. Klikovits T, Stockhammer P, Laszlo V, et al. Circulating complement component 4d (C4d) correlates with tumor volume, chemotherapeutic response and survival in patients with malignant pleural mesothelioma. *Sci Rep.* 2017;28;7(1):16456. doi: 10.1038/s41598-017-16551-7. PMID: 29184132.
10. Jumeau R, Peguret N, Bari B. D, et al. Sparing healthy lung by focusing the radiation beam flow onto the emphysematous regions in the treatment of lung cancer. *J Med Imaging Radiat Oncol.* 2017;61(2):252-257. doi: 10.1111/1754-9485.12516. PMID: 27650590.
11. Soumagne T, Chardon ML, Dournes G, et al. Emphysema in active farmer's lung disease. *PLoS One*. 2017;12(6):e0178263. doi: 10.1371/journal.pone.0178263 PMID: 28614400.
12. Avnioglu S, Unur E, Acer N, et al. Stereological measurement of liver volume in newborn cadavers. *Cukurova Medical Journal*. 2020;45(1): 223 -231 doi: 10.17826/cumj.645040.
13. W. Guan, Z. Ni, Yu Hu, et al. Clinical characteristics of 2019 novel coronavirus infection in China. *N Engl J Med*. 2020;382:1708-1720. doi: 0.1101/2020.02.06.20020974.
14. Xu X, Yu C, Qu J, et al. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2. *Eur J Nucl Med Mol Imaging*. 2020;47(5):1275-1280. doi: 10.1007/s00259-020-04735-9. PMID: 32107577.
15. Iwasawa T, Sato M, Yamaya T, et al. Ultra-high-resolution computed tomography can demonstrate alveolar collapse in novel coronavirus (COVID-19) pneumonia. *Jpn J Radiol.* 2020;38(5):394-398. doi: 10.1007/s11604-020-00956-y. PMID: 32236856.
16. Tan C, Huang Y, Shi F, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. *J Med Virol*. 2020;92(7):856-862. doi: 10.1002/jmv.25871. PMID: 32281668.
17. Cheng Z, Qin L, Cao Q, et al. Quantitative computed tomography of the coronavirus disease 2019 (COVID-19) pneumonia. *Radiol Infect Dis*. 2020. doi: 10.1016/j.jrid.2020.04.004. PMID: 32346594.
18. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. *Am J Hematol*. 2020;95 (7):834-847. doi: 10.1002/ajh.25829. PMID: 32282949.
19. Felsenstein S, Herbert JA, McNamara PS, et al. COVID-19: Immunology and treatment options. *Clin Immunol*. 2020;108448. doi: 10.1016/j.clim.2020.108448. PMID: 32353634.
20. Tang N, Bai H, Chen X, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18(5):1094-1099. doi: 10.1111/jth.14817. PMID: 32220112.
21. Tang N, Li D, Wang X, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost.* 2020;18(4):844-847. doi: 10.1111/jth.14768. PMID: 32073213.
22. Lippi G, Favaloro EJ. D-dimer is associated with severity of coronavirus disease 2019: a pooled analysis. *Thromb Haemost.* 2020;120(5):876-878. doi: 10.1055/s-0040-1709650 PMID: 32246450.
23. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020; 395(10223):497-506. doi: 10.1016/ S0140-6736(20)30183-5 PMID: 31986264.
24. Marietta M, Ageno W, Artoni A, et al. COVID-19 and haemostasis: A position paper from Italian society on thrombosis and haemostasis (SISET). *Blood Transfus.* 2020;18(3):167-169. doi: 10.2450/2020.0083-20. PMID: 32281926.
25. Lyu P, Liu X, Zhang R, et al. The performance of chest CT in evaluating the clinical severity of COVID-19 pneumonia: identifying critical cases based on CT characteristics. *Invest Radiol*. 2020;17. doi: 10.1097/RLI.0000000000000689 PMID: 32304402.
26. Shen C, Yu N, Cai S, et al. Quantitative computed tomography analysis for stratifying the severity of Coronavirus Disease 2019. *J Pharm Anal*. 2020;10(2):123-129. doi: 10.1016/j.jpha.2020.03.004. PMID: 32292624.
27. Ay MO, Kozaci N, Avci M, et al. Utility of biochemical markers and RVD/LVD ratio in acute pulmonary embolism risk classification in Emergency Department. *Eur Rev Med Pharmacol Sci*. 2017;(19):4391-4397. PMID: 29077155.