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ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2022;11(1):1-6

Evaluation of the correlation of D-Dimer tests with tomographic findings in Covid-19 patients

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Received 09 May 2021; Accepted 08 July 2021
Available online 06.01.2022 with doi: 10.5455/medscience.2021.05.161

Abstract

This study seeks to evaluate the relationship between d-dimer levels and computer tomography (CT) findings at the time of the first admission to the hospital and the effect of these examinations on the hospitalization time. Our study group consists of patients who were admitted to our hospital on an outpatient basis between 1 June and 30 July and who were hospitalized and had a positive PCR covid 19 tests. Age and gender of these patients, duration of hospitalization, first plasma D-dimer levels analyzed on the day of hospitalization, and Thoracic CT severity scores were obtained from the Hospital Information Management System (HIMS) and recorded. All these data were arranged in Microsoft Office 365 EXCEL program and evaluated statistically in SPSS 21.0 program. Patients with d-dimer levels above the cut-off value at the first admission had high CT severity scores and longer hospitalization periods. Increasing the age of the patient prolongs the hospitalization. The fact that d-dimer levels above the cut-off value at the time of first application show increased lung infiltration, will reduce the need for chest tomography in the diagnosis and follow-up of covid 19.

Keywords: D-dimer, computed tomography, Covid 19 virus

Introduction

In December 2019, "Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)" was detected in Wuhan, the People's Republic of China, caused by a new bat-borne coronavirus that can infect humans. The World Health Organization (WHO) named the disease caused by this virus "Coronavirus Disease 2019 (COVID-19)" and announced that this disease has turned into a pandemic in March 2020 [1].

Clinical forms of SARS-CoV-2 infection include a broad spectrum ranging from asymptomatic infection to mild upper respiratory tract disease, severe viral pneumonia-causing respiratory failure, sepsis, multi-organ failure, and even death [1]. SARS-CoV-2 binds to the receptor called ACE2 (angiotensin-converting enzyme 2) to enter the cell. While the organ with the most ACE2 receptor structure is the lung, these receptors are found in all endothelial structures. Therefore, in Covid 19 infection, the endothelial cells lining the inner wall of the vessels are disrupted [2]. Disruption of the endothelial structure negatively affects the coagulation process, and intravascular coagulation increases. D-dimer test is one of the parameters used to evaluate this pathological process and shows the amount of fibrin degradation products. It has been shown in many publications that intravascular inflammation and thrombosis increase d-dimer levels and that high d-dimer levels are a marker for poor prognosis for covid 19 [3].

In patients with respiratory complaints, chest radiography (X-ray) or computed tomography (CT) should be taken to see the presence and extent of pneumonia. Chest radiography is preferred because it is easier and contains less radiation, but with computed tomography, lung tissue can be seen in more detail. The severity of lung involvement determined by thorax CT is also reported to be substantial for the course of the disease [3]. In this study, the relationship between plasma d-dimer levels measured at the first admission to the hospital and the intensity of CT findings in patients who were diagnosed with covid-positive by RT-PCR and decided to be hospitalized, and its effects on the duration of hospitalization were analyzed.

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Materials and Methods

Patients who were admitted to the pandemic outpatient clinic of Usak Training and Research Hospital between 1 June and 30 July 2020 and were hospitalized with the suspicion of COVID-19 in the pandemic service and who were COVID-positive because of RT-PCR test analyzed from nasopharyngeal swab samples were recorded. Age and gender of these patients, duration of hospitalization, first plasma D-dimer levels analyzed on the day of hospitalization and scoring levels of Thoracic CT results were obtained from the Hospital Information Management System (HIMS) and recorded.

Plasma D-dimer levels of the patients were analyzed using a BCS XP (Siemens, Germany) coagulometer device with immunoturbidimetric measurement, and nasopharyngeal swab samples were analyzed using Biorad CFX 96 Touch Real-time PCR device.

Exclusion criteria included pregnancy, cancer, hematologic malignancy, chronic liver disease, acute coronary syndrome, surgery or trauma within 30 days, and patients without D-dimer testing upon admission [5].

This study was approved by the institutional ethics board of Usak University (No. 110-02-02).

All CT scans were performed with a thorax computerized tomography (CT) device (TOSHIBA Aquilion 16 CT Scanner in Kyoto, Japan) using a low-dose CT protocol. Patients were scanned in a supine position during deep inspiration. The acquisition parameters were standardized as tube voltage, 140 kV; tube current, 40 mA; pitch, 1.4; field of view (FOV), 455 mm; slice thickness, 16×5 mm. Radiological evaluation of thoracic CTs and the differentiation of Covid-19 pneumonia were made according to the Corads classification. The CT severity score was calculated by one radiologist based on the criteria in the publication "Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19)" published by Pan et al in 2020 [6]. Accordingly, the severity of the disease was classified according to the noticeable ground glass images, segmental consolidation findings, and the intensity of the involvement on CT. A semi-quantitative CT severity score was used for each of the 5 lobes of each patient. Each of the five lung lobes was assessed for degree of involvement and classified as follows (Figure 1): 0 if there is no involvement; A score of 1 for <5% involvement, 2 for 5–25% involvement, 3 for 26–50% involvement, 4 for 51-75% involvement, and 5 for> 75% involvement were given. The global CT score was created with the sum of each lobar score. All recorded data were evaluated statistically in SPSS 21.0 program.

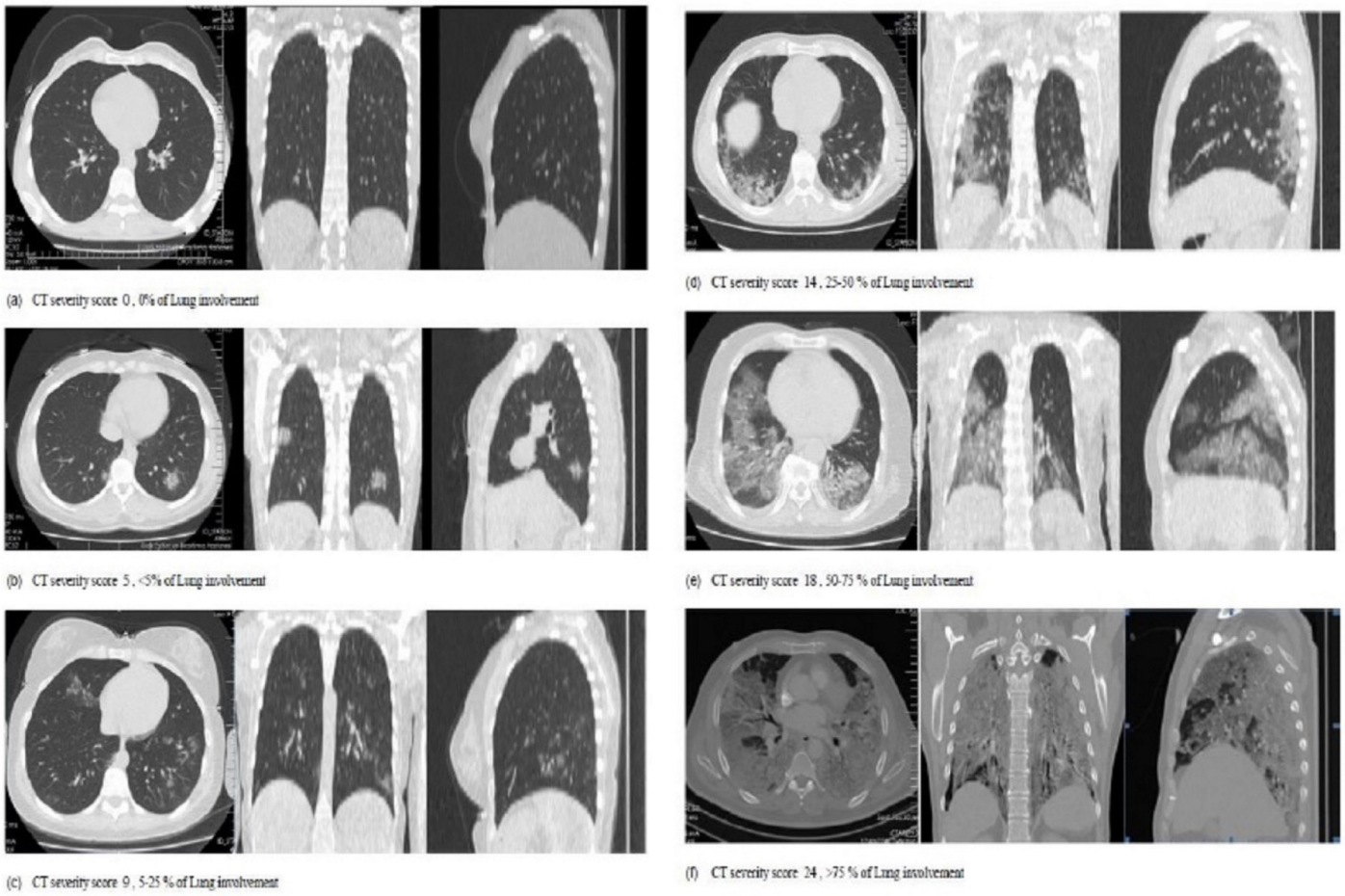

Figure 1. Different CT severity score of Lung involvement in COVID-19 pneumonia on axial, coronal, and sagittal images. 0% of Lung lobe involvement (a); < 5% of Lung involvement CTSS:5 (b); 5-25% of Lung involvement CTSS:9 (c); 25-50% of Lung involvement CTSS:14 (d); 50-75% of Lung involvement CTSS:18 (e); > 75% of RLL involvement CTSS:24 (f) High Ddimer value (3307) CT severity score:19 , 50-75 % of Lung involvement

While evaluating the study data, in addition to descriptive statistical methods (Average, Standard Deviation, Median, Frequency, Ratio, Minimum, Maximum), the distribution of the data was determined by the Kolmogorov Smirnov Test. Since all data did not show normal distribution, quantitative data were evaluated using Kruskal Wallis and Mann Whitney U tests.

Results

146 of the patients who are decided to be hospitalized and diagnosed with Covid positive are male (54.9%) and 120 are female (45.1%). Descriptive statistics of age, oxygen saturation level, duration of hospitalization, first measured D-dimer level and CT evaluation scores are shown in Table 1.

The patients in the study were subdivided according to their CT scores, age, duration of hospitalization, and plasma D-Dimer levels (Table 2).

Table 1. Descriptive statistics of study groups

Descriptive Statistics							
	N	**Mean**	**Std. Deviation**	**Median**	**Range**	**Min**	**Max**
Age	266	50.2	15.7	48.5	72	20	92
Oxygen saturation (%)	266	96.9	1.3	97	4	95	99
Duration of Hosp.	266	7.0	3.2	6	21	3	24
D Dimer Level (ng/mL)	266	691.5	720.4	498.4	4130	170	4300
CT Score	266	6.2	5.2	5	24	0	24

Table 2. Grouped data of study groups

CTSCORE	**Frequency**	**%**	**Age Group**	**Frequency**	**%**
0-4	116	43.6	20-39	69	25.9
5-9	91	34.2	40-64	142	53.4
10-14	37	13.9	>65	55	20.7
15-19	17	6.4	Total	266	100.0
20 & upper	5	1.9			
Total	266	100.0			
Duration of Hosp.	**Frequency**	**%**	**D-Dimer Level (ng/mL)**	**Frequency**	**%**
0-5 days	97	36.5	<550	150	56.4
6-9 days	128	48.1	550-1000	79	29.7
10 & more	41	15.4	>1000	37	13.9
Total	266	100.0	Total	266	100.0

D dimer results were divided into three groups as those below the reference value (<550 ng / mL), those between 550 ng/mL and 1000 ng/mL, and those >1000 ng / mL (Group 1, Group 2, Group 3, respectively); The difference between the CT scores of these groups was compared with the Kruskal Wallis test and it was observed that the CT scores of the group with D-Dimer <550 ng / mL was significantly lower than the other groups (p = 0.003) (Figure 2). Mann Whitney U test was performed for pairwise comparisons. Bonferroni correction was applied for the statistically significant p-value; p <0.017 (0.05/3) was considered significant. Accordingly, it was seen that the CT scores of Group-1 were significantly lower than the other two groups (Group1-2 p: 0.001 and Group 1-3 p: 0.002). There is no significant difference between group 2 and 3 in terms of CT score (p: 0.102).

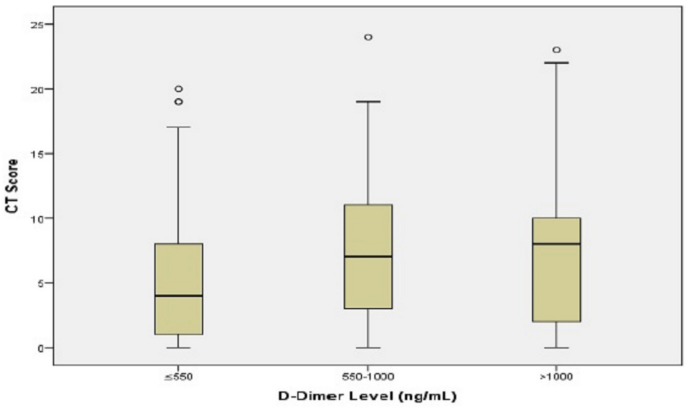

Figure 2. Box plot graphic of CT score by D-Dimer Levels

CT score per involved lobe was calculated to show the intensity of involvement. (CT Score/Number of Lobe Affected). CT score/ number of lobes involved ratio is highest at >1000 ng/mL D-dimer level (2.16) (Table 3). The most commonly involved lung lobes at all three D-Dimer levels were the Right Lower (RLL) and Left Lower (LLL) lobes. According to the CT scores, it can be said that the most intense infiltration is seen in these lobes (Table-4).

The relationship between the D-Dimer level measured at the first admission and the duration of hospitalization was examined with the Kruskal Wallis test. According to the D-Dimer levels, the average length of stay in the hospital for group 1, group 2, and group 3 was 6.5; 7.4 and 8.2 days (median values 6, 6, and 7, respectively), and there was no statistically significant difference (p=0.055) (Table 5).

The Kruskal Wallis test was applied to compare the effect of CT scores measured at the first admission on the duration of hospital stay, and it was found that there was a significant difference between the groups (Table-5). In paired group comparisons, Bonferroni correction was made for p-value, and values less than p: 0.05/6 = 0.0083 were considered significant. Accordingly, the duration of hospitalization with a CT score of <4 was found to be significantly lower (Table 5).

The hospitalization time was evaluated according to the age groups of the patients. The hospitalization time for the age groups of 20-39, 40-64, 65, and over was 6; 7; 8, respectively. and a significant difference was found with the Kruskal Wallis test (p=0.001). The hospitalization of patients under the age of 40 was found to be significantly lower (Table 5).

Table 3. The number of involved lobes (n) and their ratio (%) according to D-dimer level

			Number of Lobes Affected						Total
			0	1	2	3	4	5	
D-Dimer Level	≤550 ng/mL	n	17	24	20	13	22	54	150
		%	11.3%	16.0%	13.3%	8.7%	14.7%	36.0%	100.0%
	550-1000 ng/mL	n	4	10	4	7	7	47	79
		%	5.1%	12.7%	5.1%	8.9%	8.9%	59.5%	100.0%
	>1000 ng/mL	n	4	4	5	3	3	18	37
		%	10.8%	10.8%	13.5%	8.1%	8.1%	48.6%	100.0%
Total		Count	25	38	29	23	32	119	266
		%	9.4%	14.3%	10.9%	8.6%	12.0%	44.7%	100.0%

Table 4. The frequency of lung lobe involvement (n) - ratio (%) by the D-dimer level and total scores CT

D-Dimer Level (ng/mL)	Frequency of lobe involvement										CT Score/ Number of Lobe Affected
	RUL		RML		RLL		LUL		LLL		
	n (%)	CT Score	n (%)	CT Score	n (%)	CT Score	n (%)	CT Score	n (%)	CT Score	
<550	80 (53.3)	127	83 (55.3)	124	118 (78.7)	232	77 (51.3)	115	104 (69.3)	184	1.69
550-1000	60 (75.9)	107	54 (68.4)	97	69 (87.3)	152	60 (75.9)	104	63 (79.7)	145	1.97
>1000	22 (59.5)	44	20 (54.1)	46	30 (81.1)	74	26 (70.3)	50	27 (73)	56	2.16

(RUL: right upper lobe, RML: right middle lobe, RLL: right lower lobe, LUL: left upper lobe, LLL: left lower lobe)

Table 5. Evaluation of duration of hospitalization according to age groups, CT scores and D-dimer

	Age	n	Mean Rank	Kruskal Wallis Test	
Duration of Hospitalization	20-39	69	104.83	Chi-Square	16.642
	40-64	142	137.46	dF	2
	65 and older	55	159.25	Asymp. Sig	<0.001
	Total	266			
	CT Score				
	0-4	116	110.57	Chi-Square	19738
	5-9	91	146.79	df	3
	10-14	37	155.85	Asymp. Sig.	0.0002
	15 & Upper	22	161.84		
	Total	266			
	D-dimer				
	<550	150	124.23	Chi-Square	5.795
	550-1000	79	141.62	dF	2
	>1000	37	153.73	Asymp. Sig	0.055
	Total	266			

Discussion

In this study, we evaluated the relationship between the intensity of lung infiltration and high D-dimer levels at the time of the first admission to the hospital. In the groups that were classified according to D-dimer levels, there was a significant difference between the 1st group and the other groups in terms of CT score (Figure 3). Furthermore, there is a significant difference in the number of lobes affected and the involvement scoring levels per lobe among the D-Dimer groups.

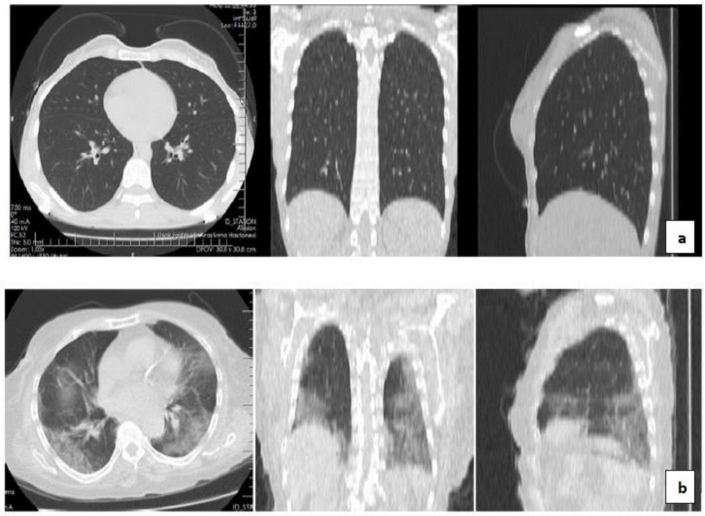

Figure 3: An example image showing the correlation low D-dimer value – low CT severity score (a), high D-dimer value – high CT severity score (b)

Figure 3. An example image showing the correlation low D-dimer value – low CT severity score (a), high D-dimer value – high CT severity score (b)

Endothelial damage occurs with the inflammatory process and the coagulation cascade begins with the released mediator molecules from endothelial. Thus, coagulation abnormalities occur associated with COVID-19. This makes clinical management difficult [8]. In COVID-19 infection, coagulopathy is first manifested by marked elevation of D-dimer and fibrin/fibrinogen degradation products [9]. This situation suggests de novo coagulopathy in COVID-19 patients. We found a significant difference between d-dimer and lung involvement levels of our patients hospitalized with covid 19 (+). At the same time, the findings support severe hypercoagulation rather than an imbalance between clotting and inflammation [10]. In the study conducted by Bilaloğlu et al among 3334 consecutive patients admitted to 4 hospitals in New York City, thrombotic events occurred in 16%, and the high levels of D-dimer at the time of admission were found to be independently associated with thrombotic events [11].

As stated by Marini et al., It has been shown that the ventilation-perfusion balance is impaired by the effect of endothelial damage caused by inflammation and edema in the alveolar space. This affects blood oxygenation, leading to the formation of hypoxia. Especially in patients with asymptomatic COVID-19 pneumonia, thoracic computed tomography (CT) is recommended because there are not always findings on chest radiography even when there are pulmonary lesions. Ground glass images and segmental consolidation draw attention to the thorax CT of these patients [12].

According to the study of Chang M et al, we found especially the right lower lobe was the most affected area and the involvement score per lobe was found to be the highest [13]. Besides, a statistically significant difference was found between the duration of hospitalization and age and CT scores. High D-dimer levels may be the result of diffuse microthrombi or be associated with the progression of the infection. Increased prevalence of lung involvement with the impairment of the immune system is associated with increased d-dimer levels [14]. Increasing susceptibility to respiratory infections such as flu with age can be associated with changes in the immune system. With age, the response of CD8 T cells to the virus decreases, and interferon 1 response is impaired. Also, studies have mentioned the connection between the activation of complement in the immune system and endothelial dysfunction. Advanced age should be treated and followed up under observation in the hospital against complications such as microvascular thrombosis and cytokine storm. For these reasons, the hospital stay of the elderly population is prolonged [15].

The strength of our study is that all radiological and laboratory examinations were performed simultaneously, at baseline and in outpatients. Because it is obvious that D-Dimer increases, and radiological infiltration findings increase in patients with progress. The limitations of our study, the number of patients with high d-dimer levels was low, and the d-dimer cut-off value didn't adjust for age.

Conclusion

The role of CT in the diagnosis of Covid 19 patients cannot dispute. however, it is not correct to use this test for screening purpose. In the patient with clinical symptoms of the respiratory system, direct radiography should be requested as a screening test in the first place. But the chest radiograph may be normal in the early stages of disease. Also, no single feature on chest radiography is diagnostic of covid-19 pneumonia. The fact that only the d-dimer is out of the reference range should give us the idea that the level of lung infiltration will be high, and it should be used as an auxiliary marker in cases where we are unstable on the chest radiograph that we primarily use for screening.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
This study was approved by the institutional ethics board of Usak University (No. 110-02-02).

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