ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA MAKALESİ

The Relationship Between Pulmonary Artery Diameter Measured by Chest CT and D-Dimer in COVID-19 Patients Admitted to the Emergency Department

Acil Servise Başvuran COVID-19 Hastalarında Toraks BT ile Ölçülen Pulmoner Arter Çapı ile D-Dimer Arasındaki İlişki

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ABSTRACT

Aim: The coronavirus disease 2019 (COVID-19) pandemic has become a global health emergency due to its rapid spread worldwide. Our study evaluated the relationship between pulmonary artery diameter and d-dimer in COVID-19 patients.

Material and Methods: Patients aged 18 years and older with International Classification of Diseases 10 diagnosis code U07.3 who were admitted to our emergency department between March 15, 2020, and November 31, 2020, were included in our study. Demographic data (age, sex), laboratory tests (polymerase chain reaction test, d-dimer level), and imaging results (chest computed tomography, computed tomography pulmonary angiography) of the patients were retrospectively analyzed using medical records and the hospital electronic record system.

Results: A total of 1654 patients were included in the study. The 30-day mortality rate was 13.7% (n=227). The most effective independent variable on 30-day mortality was 44 years of age or older. Pulmonary artery diameter and d-dimer levels were found to be higher in both the group with typical COVID-19 chest computed tomography findings and in patients who died within 30 days. However, unlike the literature, there was no significant difference in pulmonary artery diameter and d-dimer levels between patients with and without pulmonary embolism.

Conclusion: In conclusion, we found a weak positive correlation between d-dimer and pulmonary artery diameter in COVID-19 patients.

Keywords: COVID-19; d-dimer; pulmonary artery; pulmonary artery diameter

ÖZ

Amaç: Coronavirüs hastalığı 2019 (COVID-19) salgını, dünya çapında hızla yayılması nedeniyle küresel bir sağlık acil durumu haline geldi. Çalışmamız COVID-19 hastalarında pulmoner arter çapı ile d-dimer arasındaki ilişkiyi değerlendirmiştir.

Gereç ve Yöntemler: Çalışmamıza 15 Mart 2020 ile 31 Kasım 2020 tarihleri arasında acil servisimize başvuran, Uluslararası Hastalık Sınıflandırması 10'a göre tanı kodu U07.3 olan 18 yaş ve üzeri hastalar dahil edildi. Hastaların demografik verileri (yaş, cinsiyet), laboratuvar testleri (polimeraz zincir reaksiyon testi, d-dimer düzeyi) ve görüntüleme sonuçları (bilgisayarlı göğüs tomografisi, pulmoner anjiyografi bilgisayarlı tomografisi) tıbbi kayıtları ve hastane elektronik kayıt sistemi kullanılarak retrospektif olarak analiz edildi.

Bulgular: Çalışmaya toplam 1654 hasta dahil edildi. 30 günlük mortalite oranı %13,7 (n=227) idi. 30 günlük mortalite üzerinde en etkili bağımsız değişken 44 yaş ve üstünde olmaktı. Pulmoner arter çapı ve d-dimer düzeyleri hem tipik COVID-19 toraks bilgisayarlı tomografi bulguları olan grupta hem de 30 gün içinde ölen hastalarda daha yüksek bulundu. Ancak literatürden farklı olarak pulmoner embolisi olan ve olmayan hastalar arasında pulmoner arter çapı ve d-dimer düzeyleri açısından anlamlı fark bulunmadı.

Sonuç: Sonuç olarak, COVID-19 hastalarında d-dimer ile pulmoner arter çapı arasında zayıf pozitif bir korelasyon bulundu.

Anahtar Kelimeler: COVID-19, d-dimer, pulmoner arter, pulmoner arter çapı

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has become a global health emergency due to its very rapid spread around the world. The severity of the disease clinic varies from asymptomatic to rapidly progressive and fulminant (1). The presence of comorbidities, such as advanced age (≥65 years), hypertension, chronic lung disease, and cardiovascular disease, are considered to be important factors in the more severe course of the disease (2). The most common symptoms of COVID-19 are fever, cough, muscle aches or fatigue. Atypical symptoms include phlegm, headache, hemoptysis, vomiting, and diarrhea In severe cases, acute lung injury and acute respiratory distress syndrome (ARDS) can occur as a complication, sometimes in an unexpectedly short time after the onset of dyspnea (3). The most common cause of death in this disease is uncontrolled inflammation leading to hypoxemic respiratory failure.

The relation between inflammation and thrombo-inflammation and its associated complications has been described (4). Recent studies have found a direct correlation between the d-dimer level and the severity of the disease and mortality in COVID-19 patients (5). COVID-19 has been shown to have destructive effects on pulmonary and systemic vascular structures. Most of these thromboembolic events occur in the lungs (25%). During infection, viral charge and systemic inflammation may cause damage to the endothelium in pulmonary vascular structures. Increased prostaglandin levels and hypercoagulability may cause pulmonary small vessel vasoconstriction and extensive microvascular thrombosis. These may increase pulmonary artery diameter and enlargement of the heart's right structures. Studies have shown a direct correlation between pulmonary artery diameter enlargement and mortality (6–8). Therefore, early detection of pulmonary hypertension is crucial to guide appropriate treatment. Extensive lung consolidation and ARDS can cause changes in pulmonary vascularity and pulmonary artery (PA) thrombosis (9,10). Microvascular thrombosis in the pulmonary pathway is thought to cause increased pulmonary pressure, resulting in pulmonary hypertension and pulmonary artery dilatation (11).

Although computed tomography (CT) pulmonary angiography is the gold standard for the diagnosis of PA thrombosis, non-contrast chest CT is performed in COVID-19 patients frequently in the emergency department (ED). Pulmonary artery diameter measurement, which is easy to evaluate and a non-invasive option with proven efficacy, can be used as an alternative method for screening and diagnosing pulmonary hypertension (12,13). Our study aimed to evaluate the relationship between D-dimer and PA diameter measured by non-contrast chest CT in COVID-19 patients.

Material and Methods

Our study was conducted retrospectively after obtaining the approval of the local ethics committee (2020/13-42) at the emergency department of a tertiary care training and research hospital. Between March 15, 2020, and November 31, 2020, patients 18 years and older with International Classification of Diseases (ICD) 10 diagnosis code U07.3 for meaning COVID-19 disease who were admitted to the ED with suspicion of COVID-19 were reviewed through the hospital's electronic record system.

Although the diagnosis of ICD U07.3 was coded, patients with missing data, patients younger than 18 years, pregnant women, patients with negative polymerase chain reaction (PCR) test, and no typical findings related to COVID-19 in the thorax parenchyma on CT, and recurrent admissions were excluded from the study.

Demographic data (age, gender), laboratory tests (PCR test, d-dimer level), and imaging results (chest CT, CTPA) of the patients were retrospectively analyzed using medical records and the hospital electronic record system. The laboratory findings were defined according to the upper and lower limits as pathologic, recommended by the kit manufacturer. Accordingly, a level of <500 ng/mL was used as the reference for d-dimer testing. The age-adjusted d-dimer level was calculated using the formula (age x 10 ng/mL) for patients over 50 years of age (14).

All chest CT scans were performed with a non-contrast 64-detector system (Siemens Healthineers SOMATOM) using the following parameters: 110 kV, 75 mAs, 1 mm slice thickness, spiral spacing factor 1.25. All CT scans were evaluated by a single radiologist with 15 years of experience for COVID-19 findings again. According to the guidelines of the Ministry of Health of the Republic of Türkiye, CT findings in COVID-19 patients are classified into four categories; typical for COVID-19 (category 1), indeterminate for COVID-19 (category 2), atypical for COVID-19 (category 3), and without pneumonia (category 4) (15). To increase the accuracy of the analysis, chest CT findings classification categories 2 and 3 were excluded because their findings might belong to another disease other than COVID-19.

The diameter of the main pulmonary artery was measured vertically to the axis of the vessel at the level of the right pulmonary artery bifurcation in the axial plane of the thorax CT image (Figure 1).

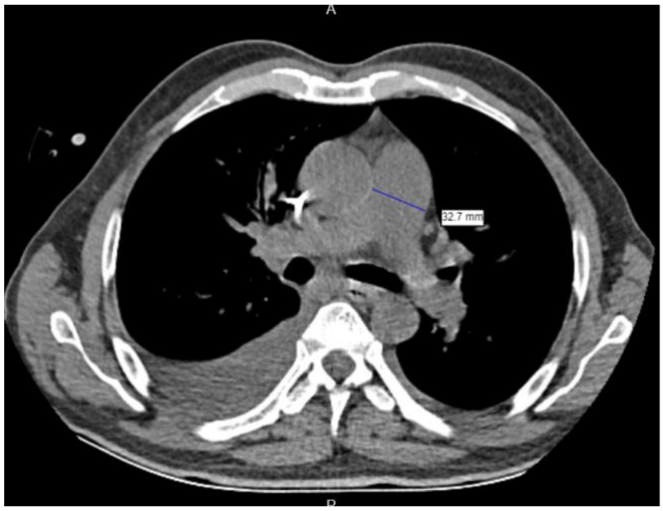

Figure 1: The diameter of the main pulmonary artery was measured vertically to the axis of the vessel at the level of the right pulmonary artery bifurcation in the axial plane of the thorax CT image.

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Using unenhanced axial CT sections, the upper limit of normal main PA diameter was accepted as ≤26.9 mm in women and ≤28.9 mm in men (16). Acute pulmonary embolism (PE) was considered to be present when CTPA showed a total filling defect in the pulmonary vessels or a central filling defect (Polo Mint sign) with contrast enhancement around it in the axial plane (17).

Statistical Analysis

SPSS for Windows Ver.20.0 (SPSS Inc., IL, USA) was used to analyze the data obtained. Data were analyzed for normal distribution using histogram, Kolmogorov-Smirnov, and Shapiro-Wilk tests. Qualitative data were expressed as numbers and frequencies, quantitative data were expressed as medians (interquartile range, minimum, and maximum). Fisher's exact and Mann-Whitney U tests were used to analyze qualitative data. Regression analysis was used for independent variables associated with mortality. All analyses were performed with 95% confidence intervals, and $p < 0.05$ was considered significant.

Results

It was determined that 7054 patients were admitted to the ED with a diagnosis of U07.3. Of these patients, 1352 were excluded from the study due to negative PCR and lack of typical chest CT findings, and 3950 were excluded due to missing data (no d-dimer test, no chest CT). The 1752 patients included in the study were considered to have COVID-19 based on PCR results and CT findings. In 98 patients with recurrent admissions, admissions other than the initial admission were also excluded. A total of 1654 patients were included in the study. While 906 of the patients included in the study had both a positive PCR test and typical chest CT findings, 459 patients had a positive PCR test but no typical chest CT findings. In 289 patients, the PCR test was negative, but typical chest CT findings were present (Figure 2).

Patients were 847 (51.2%) male, median age of 60 years (IQR=25, min=18, max=97). The PCR test was positive in 1365 (82.5%) of the patients who were included in the study.

The median d-dimer level was 755 ng/mL (IQR=1050; min=190, max=28420). The patients of 999 (60.4%) had a d-dimer level above the reference value calculated according to age. The median PA diameter was 25.9 mm (IQR=4.3; min=16.2, max=46).

A typical COVID-19-related lesion was detected on chest CT in 1195 (72.2%) patients. Pulmonary angiography CT was performed in 55 (3.3%) of the patients included in the study, and PE was detected in 12 (21.8%) of them. PA diameter was found to be higher than gender-specific limits in 500 (30.2%) of the patients. D-dimer and PA diameter were higher in patients with typical COVID-19 CT findings who died within 30 days (Table 1). The 30-day mortality rate was 13.7% (n=227). Typical COVID-19 findings were detected on chest CT in 158 (69.6%) of these patients. Of the 1654 patients who were admitted to the ED, 802 were hospitalized. 29 (4.4%) of 674 patients hospitalized in the general ward and 22 (17.2%) of 128 patients hospitalized in the intensive care unit died. It was recorded that 15 of the patients died in the ED.

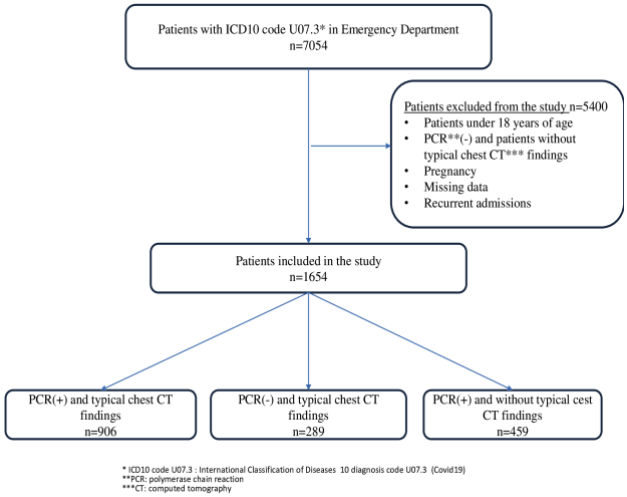

Figure 2: Flow diagram. The 1752 patients included in the study were considered to have COVID-19 based on PCR results and CT findings. In 98 patients with recurrent admissions, admissions other than the initial admission were also excluded. A total of 1654 patients were included in the study. While 906 of the patients included in the study had both a positive PCR test and typical chest CT findings, 459 patients had a positive PCR test but no typical chest CT findings. In 289 patients, the PCR test was negative, but typical chest CT findings were present.

A weakly significant positive correlation was found between d-dimer and PA diameter ($r=0.226$; $p<0.001$). There was a weakly significant positive correlation between d-dimer level above the cut-off according to age and PA diameter above the cut-off according to gender ($r=0.116$; $p<0.001$).

In the logistic regression analysis performed to determine the effect of independent variables on mortality, 30-day mortality was 2.2 times higher in male patients and 20.1 times higher in patients aged 44 years and older. It was found that a higher d-dimer level according to age and a PA diameter above the limits according to gender increased 30-day mortality by 2.8 and 2.2 times, respectively (Table 2).

Discussion

In our study, PA diameter and d-dimer levels were found to be higher in both the group with typical COVID-19 chest CT findings and in patients who died within 30 days. However, unlike the literature, there was no significant difference in PA diameter and d-dimer levels between patients with and without PE. We found a weak correlation between patients with increased d-dimer levels according to age and patients with increased PA diameter according to gender.

Numerous studies suggest that thrombotic microangiopathy affecting the pulmonary vasculature is an important pathophysiologic mechanism in severe COVID-19 disease (18). Thromboembolic events in COVID-19 pneumonia are reported to occur most frequently (25%) in the lungs (19). Studies have reported that elevated levels of d-dimer in patients with COVID-19 are suggestive of the presence of microvascular thrombus and PE (20,21).

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			D-dimer			Pulmonary artery diameter		
		n	Median (min-max) (ng/ml)	%95 CI (ng/ml)	*p*	Median (min-max) (ng/ml)	%95 CI (ng/ml)	*p*
Chest CT Classification	**Typical**	1195	810 (190-27780)	1136-1560	**<0.001**	26.1 (17.0-42.0)	26.3-26.7	**<0.001**
	Without pneumonia	207	500 (190-15020)	715-1149		24.8 (16.2-20.1)	24.7-25.7	
CTPA	Negative	43	5020 (530-28420)	4565-8605	0.463	27,2 (18.9-40.6)	26.2-29.0	0.575
	Positive	12	2725 (580-18320)	1867-9477		28,9 (19.9-30.9)	25.4-29.8	
30-days Mortality	Alive	1427	680 (190-27780)	1136-1326	**<0.001**	25.6 (16.2-45.0)	25.9-26.3	**<0.001**
	Dead	227	1600 (250-28420)	2310-3170		27.8 (17.0-46.0)	27.6-28.8	

Table 1. Analysis of d-dimer and pulmonary artery diameter according to variables.
CT: Computed tomography; CTPA: Computed tomography pulmonary angiography; min: minimum; max: maximum; CI: confidence interval.

	OR	%95 CI	*p*
44 years and older	20.112	6.367-63.527	<0.001
High age-adjusted D-dimer value	2.813	1.955-4.048	<0.001
Male	2.243	1.646-3.056	<0.001
Wide PA according to gender	2.194	1.619-2.973	<0.001

Table 2: Multivariate logistic regression analyses of variables affecting 30-days mortality.

OR:odds ratio; CI:confidence interval; PA:pulmonary artery.

Elevated laboratory parameters indicative of coagulation on hospital admission in COVID-19 patients are associated with an increased incidence of in-hospital thromboembolic events and mortality (5,22).

In a multicenter study of 1461 patients in Italy, Espasito et al. showed that d-dimer levels were higher in patients who died (23). Ippolito et al. reported that d-dimer elevation was associated with a high incidence of PE in patients hospitalized for COVID-19 infection (24). Similarly, Espallargas et al. suggested that the incidence of PE increases with increasing d-dimer concentrations (25). In our study, we found higher d-dimer levels both in patients with typical COVID-19 CT findings and in patients who died within 30 days. However, in contrast to other studies, there was no significant difference in d-dimer levels between patients with and without PE. This may be explained by the higher incidence of critical illness, infection, acute kidney injury, and extrapulmonary thromboembolic events that can cause d-dimer elevation in COVID-19 patients.

In their study, Spagnolo et al. found a median PA diameter of 31 mm (IQR 28-33 mm) in patients undergoing chest CT after COVID-19 infection, which was higher than the Framingham Heart Study reference values of 27 mm and 29 mm for women and men, respectively (26). They reported that the reason why PA diameter was found to be higher in patients who died of COVID-19 compared to those who survived might be due to factors other than PE, such as viral autoimmune endothelial damage or procoagulant abnormalities (high levels of d-dimer and fibrin degradation products, presence of antiphospholipid antibodies, prolonged prothrombin time and activated partial thromboplastin time) (20,27–29). In our study, we found higher PA diameters in patients with typical COVID-19 CT findings who died within 30 days. However, in contrast to other studies, there was no significant difference in PA diameter values between patients with and without PE.

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"Ocal et al. reported that a pulmonary artery diameter greater than 3.315 cm predicted mortality with 98% sensitivity and 89% specificity. They also found that a pulmonary artery diameter greater than 3.315 cm increased mortality by 65 times (8). Timurkaan et al. observed an increase in mortality in patients with more than 50% lung lesions. The study also reported a significant difference in pulmonary artery diameter compared with patients with less than 50% lung lesions (6). Our study also observed a significant difference in pulmonary artery diameter in patients with typical COVID-19 lesions on chest CT compared with patients without pneumonia findings. Additionally, we found that an increase in PA diameter according to gender was associated with a 2.1 times increase in mortality.

Tastemur et al. conducted a study on COVID-19 patients and found a positive correlation ($r=0.231$, $p<0.001$) between PA diameter and d-dimer (7). Another study also found a positive correlation between PA diameter and d-dimer (30). Our study observed a significant positive correlation between d-dimer and pulmonary artery diameter ($r=0.226$, $p<0.001$). D-dimer is a fibrin degradation product that suggests thrombosis in the circulation. The d-dimer level is directly correlated with the diameter of the pulmonary artery. This suggests that the increase in pulmonary artery diameter in COVID-19 patients may be related to thrombosis in the vascular circulation.

In critically ill COVID-19 patients, there were patients with limitations in CTPA application due to concomitant renal failure. Our study effectively predicts microvascular thrombosis with PA diameter and d-dimer measurement, especially in patients with CTPA limitations. Although PA diameter on non-contrast CT is higher in patients with poor prognosis, pulmonary vascular measurements on non-contrast CT scans alone may not be sufficient to decide for CTPA (26).

Limitations

The major limitation of our study is its retrospective nature. The number of patients who underwent CTPA and were found to have pulmonary embolism was small. Other limitations include the lack of data on PA diameter and pressure by right heart catheterization or echocardiography. The statistical analysis of our study was made between category 1 (typical CT findings for COVID-19) and category 4 (without pneumonia) groups in the analysis according to CT classification. Categories 2 and 3 were excluded. The PA diameter measurements of the patients were obtained during COVID-19 infection. These were not compared with any PA diameter measurements of the patient before COVID-19 infection. Comparison of PA diameter on non-contrast chest CT of the same patient before and after COVID-19 infection may be important to determine whether the increase in PA diameter is due to COVID-19 infection. Another limitation of our study is that PA diameters were measured manually. Different results may be obtained if the measurements are performed by different radiologists.

Conclusion

Increased pulmonary artery diameter and high d-dimer levels were found to be higher in both the group with typical COVID-19 chest CT findings and in patients who died within 30 days. Unlike the literature, we found a weak positive correlation between d-dimer and pulmonary artery diameter in COVID-19 patients. Our study supports that the high d-dimer levels in COVID-19 patients are associated with mortality and an increased risk of thrombosis in pulmonary and systemic vascular structures. Thoracic CT, as a non-invasive and easily accessible test, is important in predicting mortality and early treatment planning.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Ethical Approval: The study was approved by Ethics Committee of the University of Health Sciences Tepecik Training and Research Hospital, Izmir, Turkey. (Approval number 2020/13-42). All study procedures were performed in accordance with the Declaration of Helsinki.

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