Relationship between deep vein thrombosis and serial chest computerized tomography severity scores in COVID-19 patients

COVID-19 hastalarında derin ven trombozu ile seri toraks bilgisayarlı tomografi şiddet skorları arasındaki ilişkisi

Burcu Akman[1], Ahmet Turan Kaya[2], Mustafa Capraz[3], Mustafa Cihangiroglu[4]

[1] Department of Radiology, Faculty of Medicine, Amasya University

[2] Department of Radiology, Faculty of Medicine, İnönü University, Malatya, Turkey

[3] Department of Internal Medicine, School of Medicine, University of Amasya, Turkey

[4] Department of Infection Diseases and Clinical Microbiology, Medilines Hospital, Elazığ, Turkey

Abstract

Aim: We aimed to evaluate risk factors for deep vein thrombosis (DVT) in the lower extremities veins in COVID-19 patients and the relationship between DVT and chest Computed Tomography severity scores (CT-SS). To our knowledge, our study is the first to investigate the relationship between the occurrence of DVT and serial chest CT-SS in COVID-19 patients.

Methods: We retrospectively analyzed 131 COVID-19 patients (≥18 years) admitted to our hospital. Two radiologists examined chest CT scans and calculated CT-SS using a visual scoring system. Color Doppler ultrasounds of lower extremity veins were performed for DVT. CT Pulmonary Angiographies (CTPA) were performed on patients clinically suspected of pulmonary embolism (PE).

Results: A total of 131 patients were included in our study. 71/131 (54.2%) of the patients were male. 18/131 (13.7%) patients were treated in ICU, and 18 (13.7%) patients died. 21/131 (16%) patients had DVT in their lower extremities. Chest CTA was performed in 44/131 (33.6%) patients, and PE was detected in 10/44 patients (22.7%). PE was considerably more common in patients with DVT (p = 0.009). The occurrence of DVT was significantly associated with high first chest CT-SS (p=0.002). However, there was no association between the DVT and the second and third CT-SS. Significant associations were found between the development of DVT with elevated serum D-Dimer, CRP, and fibrinogen levels (p<0.001; p=0.014; p=0.031).

Conclusion: The risk of DVT is higher in COVID-19 patients with diffuse pulmonary involvement on chest CT at admission.

Keywords: Computed tomography angiography; COVID-19; doppler ultrasonography; venous thrombosis

Öz

Amaç: COVID-19 hastalarında alt ekstremite venlerinde derin ven trombozu (DVT) için risk faktörlerini ve DVT ile toraks Bilgisayarlı Tomografi şiddet skorları (BT-ŞS) arasındaki ilişkiyi değerlendirmeyi amaçladık. Bildiğimiz kadarıyla, çalışmamız COVID-19 hastalarında DVT oluşumu ile seri toraks BT-ŞS arasındaki ilişkiyi araştıran ilk çalışmadır.

Yöntemler: Çalışmamızda, retrospektif olarak hastanemize başvuran 131 COVID-19 hastayı (≥18 yaş) analiz ettik. İki radyolog toraks BT taramalarını inceledi ve görsel bir skorlama sistemi kullanarak BT-ŞS' nı hesapladı. DVT için alt ekstremite damarlarının renkli Doppler ultrasonları yapıldı. Klinik olarak pulmoner emboli (PE) olduğundan şüphelenilen hastalara BT Pulmoner Anjiyografiler (BTPA) uygulandı.

Bulgular: Çalışmamıza toplam 131 hasta dahil edildi. Hastaların 71/131'i (%54,2) erkekti. 18/131 (%13,7) hasta yoğun bakımda tedavi gördü ve 18 (%13,7) hasta öldü. 21/131 hastanın alt ekstremitelerinde DVT (%16) vardı. 44/131 (%33,6) hastaya toraks BTA yapıldı ve 10/44 (%22,7) hastada PE saptandı. DVT'li hastalarda PE sıklığı anlamlı olarak yüksekti (p= 0.009). DVT oluşumu, yüksek ilk göğüs BT-ŞS'si ile anlamlı şekilde ilişkiliydi (p=0.002). Ancak DVT ile ikinci ve üçüncü BT-ŞS arasında ilişki yoktu. Artmış serum D-Dimer, CRP ve fibrinojen seviyeleri ile DVT gelişimi arasında anlamlı ilişkiler bulundu (p<0.001; p=0.014; p=0.031).

Sonuç: Başvuru sırasında çekilen toraks BT'de yaygın akciğer tutulumu olan COVID-19 hastalarında DVT riski daha yüksektir.

Anahtar Sözcükler: Bilgisayarlı tomografi anjiografi; COVID-19; doppler ultrason; venöz tromboz

Received/*Geliş* : 31.05.2024
Accepted/*Kabul*: 11.11.2024

DOI: 10.21673/anadoluklin.1493434

Corresponding author/*Yazışma yazarı*

Burcu Akman

Amasya Üniversitesi Tıp Fakültesi, Radyoloji Anabilim Dalı, Amasya, Türkiye.
E-mail: burcuakman80@gmail.com

ORCID

Burcu Akman: 0000-0002-1067-9008
Ahmet Turan Kaya: 0000-0001-9803-453X
Mustafa Çapraz: 0000-0001-9586-6509
Mustafa Cihangiroğlu: 0000-0001-6148-5142

INTRODUCTION

Most people infected with the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus, also known as coronavirus disease 2019 (COVID-19), have a good prognosis and mild symptoms. However, in some patients, with the progression of the disease; Widespread pneumonia, pulmonary edema, acute respiratory distress syndrome (ARDS), and failure of multiple organs have occurred (1). Chest CT is one of the primary screening techniques for diagnosing and evaluating the severity of the disease (2). A visual semi-quantitative scoring method in the range of 0-25 was developed to evaluate CT severity scores (CT-SS), which define the severity of COVID-19 pulmonary involvement (3).

SARS-CoV-2 also causes thromboinflammatory disorder, and the primary prothrombotic features of COVID-19 are defined as "COVID-19-associated coagulopathy" (4). The frequency of thrombosis may increase due to endothelial injury (5) and coagulopathy (6,7). As a result of a prothrombotic imbalance in COVID-19, an increased incidence of micro and macrothrombotic events has been observed (8). Patients with COVID-19 have a higher risk of pulmonary embolism (PE) and deep vein thrombosis (DVT) (8,9). Prolonged inactivity, advanced age, intense inflammation, and post-infection hypoxia also increase the venous thromboembolism (VTE) risk (10–13). DVT and PE play an important role in morbidity and mortality, especially in severe COVID-19 patients (14).

Color Doppler ultrasound (CDUS) using compression and augmentation, and increased serum D-Dimer levels are important for the diagnosis of DVT in COVID-19 patients with increased leg diameter and temperature. Computed tomography pulmonary angiography (CTPA) should be applied to evaluate PE, especially in patients with increased heart rate and decreased arterial oxygen saturation. Some studies reported that elevated D-dimer levels had high sensitivity, ranging from 85% and 100%, but low specificity, ranging between 46% and 88.5% in the diagnosis of VTE (15–17). So, venous gray-scale and color Doppler US are the standard imaging modalities for patients with suspected DVT (18).

In studies, it has been reported that the risk of VTE is increased in patients with severe COVID-19, and severity classification is usually based on clinical symptoms. It has been reported that patients with severe COVID-19 have a 6-fold higher risk of VTE than non-severe patients (19). In a recent study, they used a CT-SS scoring system ranging from 0 to 40 and investigated the relationship between CT severity scores and thromboembolic complications secondary to COVID-19. They established that chest CT-SS was considerably higher in the group with VTE than in the group without VTE (20). In our study, we used a scoring system in the range of 0-25 when calculating chest CT-SS. Unlike studies in the literature, we calculated the CT-SS at admission and the 2nd and 3rd chest CT-SS at follow-up and evaluated its relationship with DVT. To our knowledge, our study is the first to investigate the relationship between the occurrence of DVT and serial chest CT-SS in COVID-19 patients.

In our study, we aimed to evaluate the risk factors for the development of DVT in the lower extremities in COVID-19 patients and the relationship of DVT formation with the first and follow-up chest CT severity scores.

MATERIAL AND METHODS

This study received ethical approval from the Ethical Committee of Amasya University Faculty of Medicine (date: 06.05.2021, decision no: 62) and was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice. Because the study was retrospective, patient information was gathered from the hospital's electronic records, and the ethical committee waived the requirement for written informed consent from participants.

Study population

In our study, the data of patients (≥18 years) with positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) tests (Bio-Speedy Direct qRT-PCR SARS-CoV-2, Bioeksen, Turkey) who were applied to our hospital between January 1 and June 15, 2021, were examined.

Inclusion criteria: Patients older than 18 years of age, with a positive RT-PCR test, and who underwent

chest CT and CDUS were included in the study. In addition, patients who performed CTPA because of suspicion of PE were included in the study.

***Exclusion criteria**:* Patients under 18 years of age, without RT-PCR test results, chest CT and CDUS, serum D-Dimer levels, and patients with negative RT-PCR test results were excluded from the study (Figure 1).

Clinical and laboratory data

The demographic data of patients, comorbidities, and laboratory findings of every patient acquired within a day following the date of lower extremity venous CDUS, hospital and/or intensive care (ICU) admission, and mortality were recorded from the electronic medical records of our hospital. Serum D-dimer levels ≥ 0.50 μg/mL were considered an increased value.

Color doppler US protocol

Color Doppler US scans of the lower extremity veins were applied using Mindary Digital Ultrasound Imaging System (Model DC-8; Shenzhen Mindray Biomed Electronics, Shenzhen, China). We used a linear vascular transducer (Frequency: 6.5 MHz; Range: 2.6-8.2 MHz) for CDUS of the lower extremity venous system.

CT protocol

The patients' chest CT and CTPA images were acquired on the multi-detector CT (MDCT) scanner 128-slice GE Healthcare Revolution EVO CT (GE Medical Systems; Milwaukee, WI). The non-contrast chest CT parameters: tube current, 100–450 mA; tube voltage, 120 kV; slice thickness, 0.625 mm. Chest CT scans were performed on patients who were resting supine and holding their breath after a deep inspiration. Scans were performed from the apex to the end of the lung, including all bilateral lung parenchymas.

To examine PE in patients with severe dyspnea, elevated blood D-dimer levels, and an abnormal ECG, CT Pulmonary Angiography (CTPA) was done following the injection of 80 mL of high-concentration iodine contrast agent (Iohexol 350 mgl/l) at a flow rate of 4 ml/sec. The CT scan settings were as follows: tube voltage, 100 kV; beam collimation, 64 mm × 0.625 mm; and the mean tube current was 400 mA.

CT imaging analysis

Two radiologists, blinded to the clinical data and laboratory findings, and with 10 and 16 years of experience, evaluated the first chest CT and, if available, second and third chest CT images. The radiologists calculated the CT severity scores (CT-SS) that defined the severity of COVID-19 pulmonary involvement using the predefined visual semi-quantitative scoring method (3). Scoring was performed according to the percentage of parenchymal involvement in the range of 0-5 per lobe (0 = 0.1% = 1% - 5.2%, 2% = 6% - 25%, 3 = 26% - 50%, 4 = 51% - % 75 and 5 => 75%), and the scores were summed to obtain total CT-SS (range from 0 to 25). The radiologists evaluated the proximal and evaluable distal branches of both pulmonary arteries for the presence of a thrombus, which was seen as a filling defect in the lumens in CTPA scans.

Color doppler US imaging analysis

Two radiologists with 10 and 16 years of experience performed CDUS in consensus on both lower extremity veins of COVID-19 patients. Each patient's lower extremity veins were evaluated for DVT starting from the inguinal ligament to the ankle. Bilateral lower extremity veins were examined from the main femoral veins to the end of the crural veins (anterior tibial, posterior tibial and peroneal veins). To evaluate the presence of thrombus in the US, vessel probe compression was applied at 1–2 cm intervals, and color Doppler imaging and Spectral Doppler waveforms were used. The augmentation maneuver was performed by quickly squeezing the leg below the insonation level. During the maneuver, the rapid increase in blood flow on spectral Doppler US was considered a normal response, and a thrombus below the insonation level was excluded. CDUS revealed deep vein thrombosis as increased venous diameter (often larger than an adjacent artery) and little or no blood flow in the lumen. The thrombus appears anechoic or hypoechoic in comparison to the neighboring muscle tissue, and the vessel does not collapse during the compression test (21).

Statistical analysis

Data was analyzed using IBM Statistical Package for the Social Sciences package program version 22.0 (IBM

Corp., Released 2017, Armonk, NY). Using the Kolmogorov-Smirnov test of normality, it was examined whether the variables were normally distributed. In descriptive analyses, non-normally distributed variables were represented by the median and interquartile range (IQR), whereas regularly distributed variables were represented by the mean and standard deviation. When comparing continuous variables based on the existence of DVT, the Student t-test was employed for those with normal distribution, and the Mann-Whitney U test for those without normal distribution. Instead of comparing categorical variables based on the presence of DVT, Chi-Square or Fisher's tests (if the values given in the cells did not match the Chi-Square test assumptions) were employed. In pairwise comparisons based on DVT presence or absence, the paired samples test or the Wilcoxon signed-rank test was utilized. When there were fewer than 30 cases and no parametric assumptions were available, the Wilcoxon signed-rank test was utilized. A p-value of <0.05 was judged statistically significant.

RESULTS

The study population included 131 patients with a mean age of 63.21±13.51 years; 71/131 (54.2%) were male. Of all 131 patients, 19/131 (14.5%) patients were treated as outpatients, 18/131 (13.74%) patients were treated in the ICU, and 18/131 (13.74%) patients died. In CDUS, 21/131 patients had DVT (16%) in their lower extremities. Of this subgroup, 18/21 (85.71%) patients had unilateral DVT, and 3/21 (14.29%) patients had bilateral DVT. In the group of patients with DVT, 10/21 (47.62%) patients were male with a mean age of 63.81±12.51 years. Age and gender did not show a significant relationship with DVT (p=0.826, p=0.509).

4/21 (19.05%) patients died in patients with DVT, which was higher than those without DVT. However, there was no significant difference between the groups with or without DVT with death and ICU admission (p=0.489, p=0.737). DVT was significantly associated with ground-glass opacity (GGO) (p=0.014) and CT findings of more complicated pneumonia, such as halo sign (p=0.036), reversed halo sign (p=0.001), crazy paving pattern (p=0.001), interlobular septal thickening (p=0.028). The study population's most common comorbidity was cardiovascular disease (88/131; 67.2%), chronic pulmonary disease (35/131;26.7%) and diabetes mellitus (DM) (32/131;24.4%) in total patients. There was no significant association between the occurrence of DVT in the lower extremities and comorbidities. CTPA was performed on 44/131 (33.59%) patients with suspected PE. Of these patients, 10/44 (22.7%) had PE. 5/10 (50%) of patients with PE also had DVT. Patients with DVT had a noticeably greater frequency of PE (p=0.009) (Table 1).

The mean first, second and third CT-SS of the total patients was 7.10±6.997; 13.73±7.452; 14.61±7.95. The mean first CT-SS value in the group with DVT was 10.86±6.04, which was significantly higher than those without. So, the occurrence of DVT was significantly associated with high first chest CT-SS (p=0.002). However, there was no significant relationship between the second and third CT-SS and DVT formation (p=0.831; p=0.572) (Figure 2). In addition, significant associations were found between DVT with elevated D-Dimer levels obtained at admission and on the day of CDUS (both p<0.031) and CRP levels at admission and serum fibrinogen levels on the day of CDUS (p= 0.014; p= 0.031) (Table 2).

In paired comparisons, the increase in the first and second chest CT severity score was significant in the group without DVT (p<0.001), but it was insignificant in patients with DVT (p=0.075). In both patient groups with and without DVT, d-Dimer levels on the day of Doppler US were significantly increased compared to the levels at admission (p=0.046; p=0.001). Additionally, in the group without DVT, a significant increase in CRP level was detected from hospital admission to the day of Doppler US. However, since the level of the first CRP is higher in the DVT group, no significant increase was seen between the first and second CRP levels (Table 3).

DISCUSSION AND CONCLUSION

In our study, we investigated the risk factors for the development of DVT in the lower extremities veins and the effect of periodic changes in pneumonia severity on the development of DVT in COVID-19 patients. We found a significant positive correlation between the development of DVT and the first CT-SS. How-

Table 1. Comparison of demographic parameters and CT findings according to the presence of deep vein thrombosis

		Deep vein thrombosis					
		Absent		Present		Total	
		n	(%)	n	(%)		p value
Gender	Female	49	81.7	11	18.3	60	0.509
	Male	61	85.9	10	14.1	71	
Death or alive*	Alive	96	85	17	15	113	0.489
	Death	14	77.8	4	22.2	18	
Inpatients or outpatients*	Outpatients	17	89.5	2	10.5	19	0.737
	Inpatients	93	83	19	17	112	
ICU*	Non- ICU	78	83.0	16	17.0	94	0.999
	ICU	15	83.3	3	16.7	18	
Pulmonary embolism*	Absent	31	91.2	3	8.8	34	0.009
	Present	5	50	5	50	10	
GGO*	Absent	35	97.2	1	2.8	36	0.014
	Present	75	78.9	20	21.1	95	
Consolidation	Absent	80	86	13	14	93	0.317
	Present	30	78.9	8	21.1	38	
Crazy paving pattern	Absent	82	91.1	8	8.9	90	0.001
	Present	28	68.3	13	31.7	41	
Reticular pattern*	Absent	53	94.6	3	5.4	56	0.006
	Present	57	77	17	23	74	
Reversed halo present	Absent	87	90.6	9	9.4	96	0.001
	Present	23	65.7	12	34.3	35	
Halo present	Absent	64	90.1	7	9.9	71	0.036
	Present	46	76.7	14	23.3	60	
Intralobular septal thickening	Absent	58	90.6	6	9.4	64	0.061
	Present	52	78.8	14	21.2	66	
Interlobular septal thickening*	Absent	52	92.9	4	7.1	56	0.028
	Present	58	78.4	16	21.6	74	
Vascular Thickening	Absent	37	90.2	4	9.8	41	0.212
	Present	73	81.1	17	18.9	90	
Mosaic attenuation	Absent	84	88.4	11	11.6	95	0.048
	Present	26	74.3	9	25.7	35	
Pericardial effusion*	Absent	91	84.3	17	15.7	108	0.764
	Present	19	82.6	4	17.4	23	
Pleural Effusion*	Absent	101	84.9	18	15.1	119	0.407
	Present	9	75	3	25	12	
Adjacent pleural thickening*	Absent	57	93.4	4	6.6	61	0.013
	Present	53	76.8	16	23.2	69	
Bronchial wall thickening*	Absent	43	93.5	3	6.5	46	0.044
	Present	67	79.8	17	20.2	84	
Bronchiectasis	Absent	68	91.9	6	8.1	74	0.008
	Present	42	75	14	25	56	
Chronic pulmonary diseases	Absent	83	86.5	13	13.5	96	0.198
	Present	27	77.1	8	22.9	35	
Cardiovascular disease	Absent	37	86	6	14	43	0.651
	Present	73	83	15	17	88	
Neurological diseases*	Absent	99	84.6	18	15.4	117	0.698
	Present	11	78.6	3	21.4	14	
Diabetes mellitus*	Absent	82	82.8	17	17.2	99	0.782
	Present	28	87.5	4	12.5	32	
Kidney diseases*	Absent	108	83.7	21	16.3	129	0.999
	Present	2	100	0	0	2	
Liver diseases*	Absent	107	83.6	21	16.4	128	0.999
	Present	3	100	0	0	3	

GGO: Ground-glass opacity

Chi-square or (*) Fisher tests were used to compare categorical variables according to the presence of DVT.

n: Number, %: Percent, ICU: Intensive care unit

Table 2. Comparison of the presence of deep vein thrombosis with age, CT-SS and laboratory data

	DVT	n	Mean	SD	Min.	Max.	50th	25th	75th	p value
Age	*Absent*	110	63.1	13.74	33	89	65	52	72	0.826
	Present	21	63.81	12.51	36	83	64	57.5	74	
	Total	131	63.21	13.51	33	89	65	54	72	
First CT-SS*	*Absent*	110	6.38	6.96	0	25	4.5	0	10	0.002
	Present	21	10.86	6.04	0	21	11	5	15	
	Total	131	7.1	7	0	25	5	1	12	
Second CT-SS*	*Absent*	110	13.66	7.45	0	25	14	7.75	20	0.831
	Present	21	14.05	7.62	0	25	14	10	20.5	
	Total	131	13.73	7.45	0	25	14	8	20	
Third CT-SS*	*Absent*	56	14.86	8.15	0	25	16.5	8.25	21.75	0.572
	Present	10	13.2	6.92	5	25	12	8.75	16.75	
	Total	66	14.61	7.95	0	25	14.5	8.75	21.25	
First D-dimer (0-0.5; µg/mL)	*Absent*	110	1.14	2.21	0	16.16	0.59	0	0.94	<0.001
	Present	21	4.35	7.27	1	32	1.82	1	3.21	
	Total	131	1.66	3.69	0	32	0.69	0	1.31	
Second D-dimer	*Absent*	110	4.14	9.5	0	58.46	1.12	1	2.78	<0.001
	Present	21	7.32	8.63	1	37.7	5.08	1	11.27	
	Total	131	4.65	9.41	0	58.46	1.31	1	3.68	
First PLT (173-360; 10U/l)	*Absent*	110	225.7	88.27	57	477	202	158.5	282.5	0.528
	Present	21	212.29	93.07	119	505	189	152.5	233	
	Total	131	223.55	88.83	57	505	193	157	268	
Second PLT	*Absent*	92	299.64	114.42	29	616	287.5	217.75	380.75	0.081
	Present	19	246.16	147.28	123	758	217	154	275	
	Total	111	290.49	121.61	29	758	267	208	380	
First PT (12-16.5 sec)	*Absent*	110	14.88	5.55	11.5	64.8	13.85	12.98	14.77	0.635
	Present	21	14.3	1.65	11.5	17.6	14	13.15	15.35	
	Total	131	14.79	5.13	11.5	64.8	13.9	13	14.8	
Second PT	*Absent*	83	15.3	3.26	11.5	27.7	14.4	13.2	16	0.253
	Present	15	18.06	8.89	13.3	49	14.8	14.3	18.3	
	Total	98	15.72	4.63	11.5	49	14.5	13.38	16.38	
First INR (0.88-1.3)	*Absent*	110	1.14	0.57	0.09	5.07	1.02	0.95	1.12	0.588
	Present	21	1.07	0.13	0.85	1.36	1.04	0.98	1.14	
	Total	131	1.12	0.52	0.09	5.07	1.02	0.95	1.12	
Second INR	*Absent*	83	1.29	0.88	0.86	6.7	1.08	1	1.2	0.558
	Present	15	1.16	0.14	0.99	1.54	1.12	1.08	1.2	
	Total	98	1.27	0.81	0.86	6.7	1.09	1.01	1.2	
First aPTT (26-40 sec)	*Absent*	110	29.2	4.85	19.3	58.8	29	26.1	31.73	0.979
	Present	21	29.23	3.73	19.1	36	29.4	27.65	31.95	
	Total	131	29.21	4.68	19.1	58.8	29.2	26.2	31.7	
Second aPTT	*Absent*	83	29.62	6.5	17.8	58.8	28.5	26	31.4	0.31
	Present	14	31.95	13.82	20.8	77.5	28.5	24.98	33.2	
	Total	97	29.95	7.91	17.8	77.5	28.5	25.75	31.5	

First Fibrinogen (200-400; mg/dl)	*Absent*	110	556.42	174.07	222	1200	547	421.5	674	0.425
	Present	21	531.56	119	319	749	528	428	614.5	
	Total	131	552.44	166.34	222	1200	542	422	660	
Second Fibrinogen	*Absent*	89	529.16	180.19	150	966	510	403	683	0.031
	Present	18	428.17	172.84	12	735	465.5	297.25	536.5	
	Total	107	512.17	182.17	12	966	498	393	647	
First CRP (0-5; mg/L)	*Absent*	110	45.09	54.83	0.1	263	22.52	9.79	65.04	0.014
	Present	21	77.96	57.83	3.3	187.85	76.83	27.43	125.59	
	Total	131	50.36	56.41	0.1	263	24.97	10.05	76.83	
Second CRP	*Absent*	91	85.79	94.98	0.05	437	66.24	7.26	141.61	0.131
	Present	19	51.31	56.68	0	179.25	27.55	6.4	96.96	
	Total	110	79.84	90.28	0	437	52.01	6.93	123.58	
Ferritin (22-322; ug/L)	*Absent*	110	285.64	365.4	5.2	2224	171.1	66.03	360.25	0.526
	Present	21	338.52	242.36	13.5	963	342.6	175.95	464.95	
	Total	131	294.11	348.38	5.2	2224	206.2	68.8	386	
ESR. (0-30; mm/H)	*Absent*	110	47.37	28.82	5	115	43	21.75	69.25	0.815
	Present	21	48.52	18.59	18	101	49	35.5	61	
	Total	131	47.55	27.38	5	115	44	24	63	
Neutrophil count (1.65-4.97; 10U/l)	*Absent*	110	6.13	6.92	1.12	69	4.72	3.46	6.7	0.683
	Present	21	6.77	4.04	2.51	16.13	5.42	3.38	9.51	
	Total	131	6.24	6.53	1.12	69	4.74	3.44	7.02	
Lymphocyte count (1.17-3.17; 10U/l)	*Absent*	110	1.4	0.82	0.16	4.52	1.26	0.8	1.79	0.416
	Present	21	1.56	0.89	0.46	4.64	1.31	1.13	2.05	
	Total	131	1.42	0.83	0.16	4.64	1.28	0.83	1.81	
Cholesterol (0-200; mg/dl)	*Absent*	86	162.94	43.91	68	278	155.5	129.75	198.25	0.923
	Present	18	161.83	45.09	87	243	158.5	121.25	190.5	
	Total	104	162.75	43.9	68	278	155.5	129.25	197.5	
SCr (0.7-1.2; mg/dl)	*Absent*	110	0.99	0.44	0.48	4.65	0.9	0.79	1.12	0.141
	Present	21	1.14	0.42	0.57	2	1.08	0.8	1.45	
	Total	131	1.01	0.44	0.48	4.65	0.92	0.8	1.14	

SD: Standard Deviation, Min: Minimum, Max: Maximum, CT-SS: CT Severity Score, aPTT: Activated partial thromboplastin time, CRP: C Reactive Protein, ESR: Erythrocyte sedimentation rate, PT: Prothrombin time, SCr: Serum creatinine
* Mann-Whitney U test was used
DVT: Deep vein thrombosis, n: Number, PLT: Platelet, sec:second, INR: International normalized ratio

ever, no relationship was found between DVT formation and the second and third CT-SS (Figure 3). Since the first chest CT-SS was higher in the patients with DVT, no significant increase was observed between the first and second CT-SS in pairwise comparisons. According to our results, severe lung involvement at the beginning of the disease increased the risk of DVT. In addition, pulmonary embolism is more frequent in patients with DVT. Significant associations were found between DVT with elevated D-dimer, CRP, and fibrinogen levels. We found no association between DVT formation and ICU hospitalization, and mortality.

Venous thromboembolism (VTE) is a common complication in severe COVID-19 patients and may cause morbidity and mortality (22). In COVID-19 patients, pulmonary-related coagulopathy, hemostatic disorders, mechanical ventilation, immobility, comorbidity, etc., are involved in the physiopathology of thromboembolism. In previous studies, advanced age, smoking, obesity, immobilization, previous VTE history, comorbidities, ICU hospitalization, intense inflammation, and hypoxia were reported among the causes that increase the risk of VTE in patients with COVID-19 (10–13,23,24). These factors cause inflam-

Table 3. Paired comparisons of CT-SS and laboratory findings according to the presence of deep vein thrombosis

	Deep vein thrombosis							
	Absent				Present			
	n	Mean	SD	p value	n	Mean	SD	p value*
Pair 1								
First CT-SS	110	6.38	6.96	<0.001*	21	10.86	6.04	0.075
Second CT-SS	110	13.66	7.45		21	14.05	7.62	
Pair 2								
Second CT-SS	56	13.82	7.62	0.319*	10	14.80	6.20	0.231
Third CT-SS	56	14.86	8.15		10	13.20	6.92	
Pair 3								
First D-dimer (0-0.5; µg/mL)	110	1.14	2.21	0.001	21	4.35	7.27	0.046
Second D-dimer	110	4.14	9.50		21	7.32	8.63	
Pair 4								
First PLT (173-360; 10^9/l)	92	230.72	90.76	<0.001	19	214.47	94.80	0.144
Second PLT	92	299.64	114.42		19	246.16	147.28	
Pair 5								
First PT (12-16.5 sec)	83	15.04	6.09	0.645	15	14.57	1.84	0.127
Second PT	83	15.30	3.26		15	18.06	8.89	
Pair 6								
First INR (0.88-1.3)	83	1.15	0.64	0.127	15	1.09	0.15	0.229
Second INR	83	1.29	0.88		15	1.16	0.14	
Pair 7								
First aPTT (26-40 sec)	83	29.07	5.37	0.457	14	29.63	4.04	0.519
Second aPTT	83	29.62	6.50		14	31.95	13.82	
Pair 8								
First Fibrinogen (200-400; mg/dl)	89	555.64	169.63	0.042	18	539.85	115.47	0.016
Second Fibrinogen	89	529.16	180.19		18	428.17	172.84	
Pair 9								
First CRP (0-5; mg/L)	91	40.30	49.12	<0.001	19	79.64	60.29	0.162
CRP	91	85.79	94.98		19	51.31	56.68	

SD: Standard Deviation, Min: Minimum, Max: Maximum, CT-SS: CT Severity Score, aPTT: Activated partial thromboplastin time, CRP: C Reactive Protein, ESR: Erythrocyte sedimentation rate, PT: Prothrombin time, SCr: Serum creatinine
Paired Samples Test and (*) Wilcoxon Signed Ranks Test were used. (Wilcoxon signed-rank test was used when the number of cases was less than 30 and parametric assumptions could not be provided.)
n: Number, PLT: Platelet, INR: International normalized ratio

matory cytokine release, platelet activation, and endothelial damage. As a result, it is thought that the risk of thrombosis and mortality increases as the disease becomes more serious (25).

The incidence ranges of DVT and PE in COVID-19 studies were reported as 7.1-35% and 12.1%-16.5%, respectively (26–28). Based on postmortem studies, approximately 10% of COVID-19-attributed fatalities have been estimated to be caused by pulmonary embolism (29). In our study, the incidence of DVT in the lower extremity veins and PE was 16% (21/131) and 7.63% (10/131) in the total study population. We included critical and non-critical COVID-19 patients in our study and CTPA was administered not to all patients, only to 44 (33.59%) patients with suspected PE. Of these patients, 10/44 (22.7%) had PE.

Many studies have reported an increased risk of VTE in severe COVID-19 patients, and severity classification is generally based on clinical symptoms. It has been reported that patients with severe COVID-19 have a 6 times greater risk of VTE than those who are not severe (19). The severity of COVID-19 pneumonia can be determined by CT-SS, which is crucial for predicting the patient's prognosis. According to Zhou et al., COVID-19 patients who died had a substantially greater total CT-SS than those who recovered (30). Francone et al.

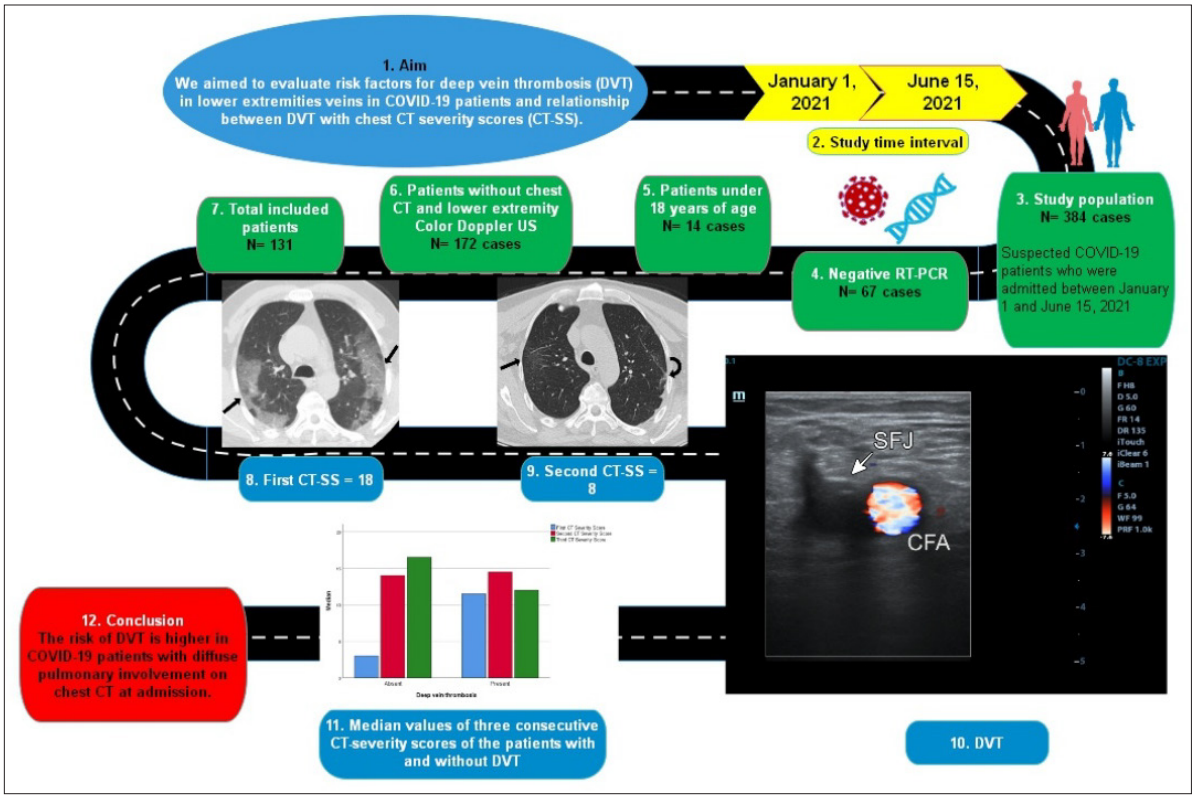

Figure 1. Workflow diagram of the study
SFJ: Saphenofemoral junction, CFA: Common femoral artery

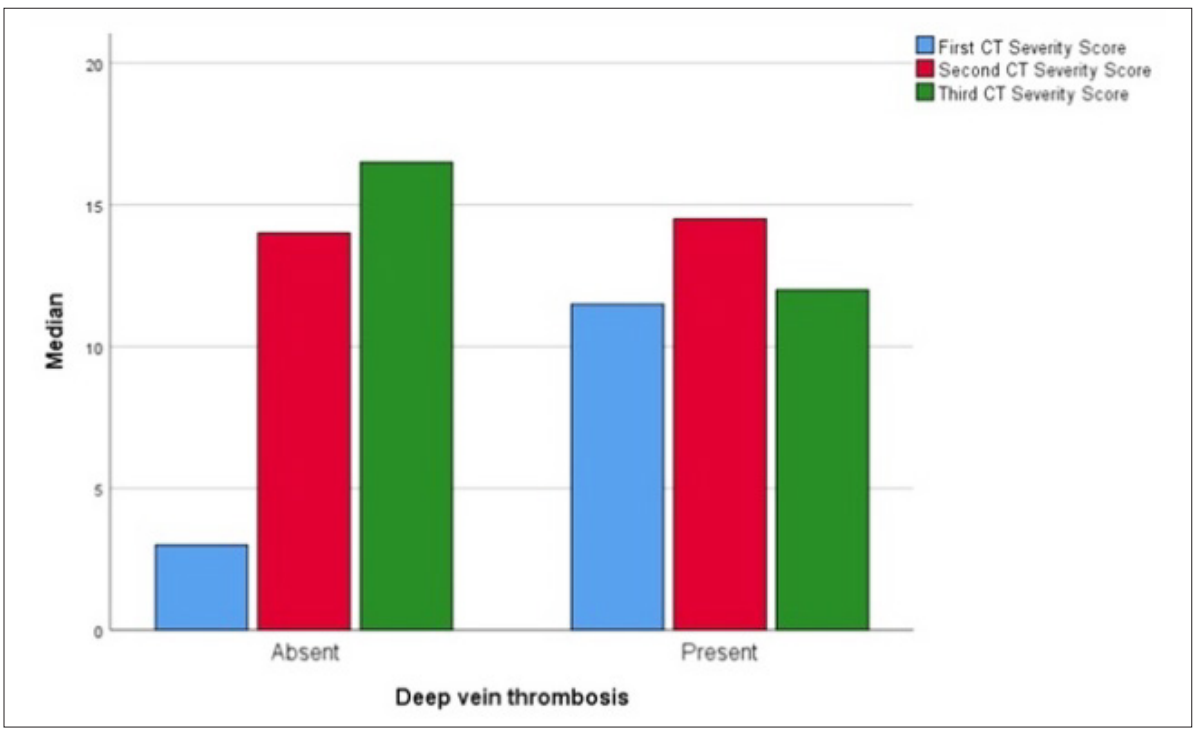

Figure 2. The statistical graphic shows the median values of three consecutive CT severity scores of the patients with and without DVT.
CT: Computed tomography, DVT: Deep vein thrombosis

reported that CT-SS was significantly higher in patients with critical and severe COVID-19 compared to the mild stage (31). Espallargas et al. assigned a score of 1 to 4 for the severity of pulmonary parenchymal involvement rates on chest CTs and examined patients' CTPA. They detected significantly higher pulmonary parenchymal scores in severe COVID-19 patients evolving from PE (32). However, Fang et al. found no difference in radiological severity in subgroups of patients with and without PE (33). In a recent study, they used a scoring system ranging from 0 to 40 points to calculate CT-SS and grouped patients according to the scores as mild, moderate, and severe. They investigated the correlation between CT severity scores and thromboembolic complications secondary to COVID-19. Chest CT-SS was significantly higher in the group with VTE than in the group without VTE (20). In our study, we used a scoring system in the range of 0-25 when calculating chest

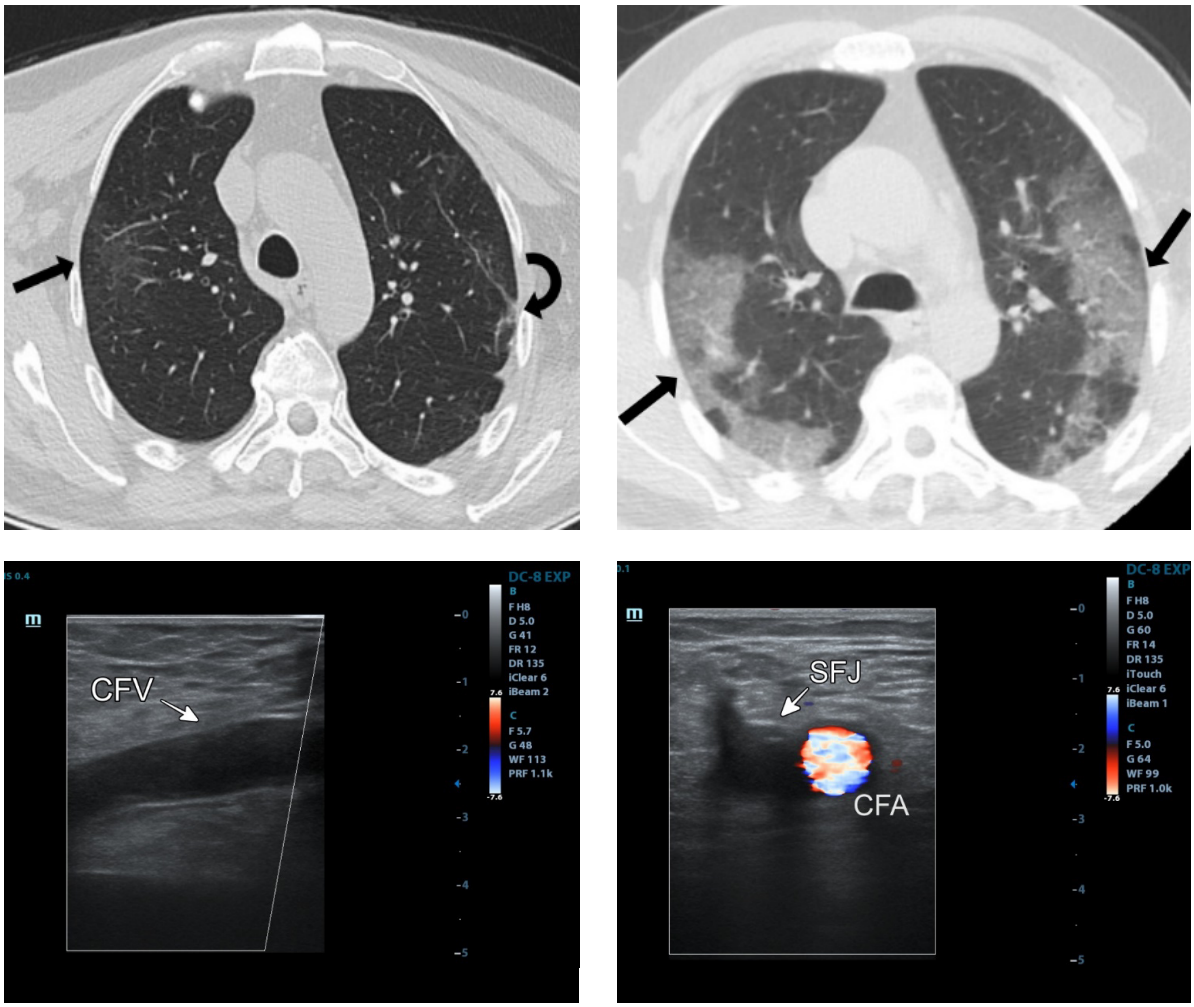

Figure 3. A 66-year-old man with a positive RT-PCR test. He was hospitalized after the first CT and treated in non-ICU in our hospital for 22 days.
(a) Axial lung window of non-contrast first chest CT shows bilateral peripherally located ground-glass opacities (straight black arrows). CT severity score=18
(b) Axial lung window of non-contrast second chest CT (20 days after first chest CT) shows minimal ground-glass opacities (straight black arrow) in the right upper lobe and intra and interlobular septal thickening (curved black arrow) in the left upper lob. CT severity score=8
(c), (d) Two days after hospitalization, he had swelling in both lower extremities. Venous Color Doppler US for the diagnosis of DVT was applied to both lower extremities. Gray scale US showed anechoic-hypoechoic thrombus in the acute phase that increased the diameter of the vein, and could not be compressed. Axial (c) and sagittal (d) planes of the color Doppler US showed no flow in the lumen of the saphenofemoral junction and common femoral vein (straight white arrows). (Saphenofemoral junction; CFV: Common femoral vein; CFA: Common femoral artery)

CT-SS. Unlike studies in the literature, we calculated the CT-SS at admission and the 2nd and 3rd chest CT-SS at follow-up and evaluated its relationship with DVT. In our study, chest CT-SS at the time of admission was significantly higher in patients with DVT compared to patients without DVT. Since the first chest CT-SS was higher in the patients with DVT, no significant increase was observed between the first and second CT-SS in pairwise comparisons. However, no significant relationship was found between DVT and the second and third chest CT-SS. This showed us that the risk of DVT is higher, especially in patients with extensive pulmonary involvement in the early period. In pairwise comparisons, there was a substantial rise between the first and second CT-SS since the first CT-SS of patients without DVT was low.

Most studies reported an increased risk of VTE in patients who were admitted to the ICU due to nutritional deficiencies, immobilization, mechanical ventilation and indwelling venous and arterial catheters (34–38). We found no relationship between ICU hospitalization and DVT formation. Patients who were treated at the hospital other than the ICU could not be mobilized as much as the intensive care patients, since their condition was generally serious. Also, there was no significant difference between mortality rates in patients with and without DVT. As a result of the anticoagulant treatment applied in our hospital, there was no increase in death rates in patients with DVT.

Some studies have reported high D-dimer levels, low lymphocyte count, or high neutrophil/lymphocyte ratio and prolongation of coagulation time among the risks of VTE.

They reported that increased serum D-dimer level was the strongest predictor of VTE among them (15,36). Many studies have been conducted to evaluate serum d-dimer levels as a prognostic indicator for VTE in COVID-19 patients. Typically, VTE can be excluded when the dimer is < 0.5 μg/mL (39). Li et al. reported an increased risk of VTE when dimer levels > 2.07 μg/mL (19). Some studies reported that elevated D-dimer levels had high sensitivity, ranging from 85% and 100%, but low specificity ranging between 46% and 88.5%, in the diagnosis of VTE (15–17). Low specificity is most likely due to increased d-dimer levels secondary to inflammatory and infectious processes in COVID-19 patients (39). Therefore, if there are no clinical symptoms of acute VTE in COVID-19 patients with high serum D-dimer values, the possibility of a false-positive should be considered and evaluation for acute VTE may not be necessary (40). Studies have reported that higher CRP levels increase the risk of VTE between 1.03 (41) and 2.71-fold (42). In our study, compatible with the literature, patients with DVT had higher serum D-dimer levels at admission and on the day of CDUS. Also, patients with DVT had higher serum CRP levels at admission serum fibrinogen levels on the day of CDUS.

In the prophylaxis of VTE, antiplatelet and anticoagulant drugs are used. Anticoagulant therapy was supported by the demonstration of a lower mortality rate in COVID-19 patients treated with thromboprophylaxis (43). Our patients (except for outpatients) were given prophylactic anticoagulation treatment after the diagnosis of COVID-19. Taking anticoagulant therapy reduces the frequency of PE (25). In our study, CTPA was not applied to all patients. CTPA was applied to patients with clinically suspected PE. A higher incidence of PE was reported in studies in which CTPA was applied to all patients (25). In our study, 50% of the patients with PE did not have DVT. Similarly, Suh et al. reported more than half of the patients with PE did not have DVT (25).

Zhou et al. reported an increased risk of VTE severity and death in patients with comorbidities such as hypertension, cardiovascular disease, kidney disease, chronic respiratory disease, cerebral vascular disease, malignancy, diabetes, and obesity in their meta-analysis (44). However, in many studies, no significant difference was reported in the incidence of VTE between patients with and without cardiovascular disease, kidney disease, cerebral disease, vascular disease, diabetes, or obesity (19,34,45,46). We also found no significant association between the occurrence of DVT in the lower extremities with comorbidities.

Males were shown to have a considerably higher risk of having DVT in COVID-19 people (OR, 2.27; P=0.035). However, age did not affect the occurrence of DVT (47). While some studies have reported a high incidence of VTE in elderly patients (19,45), other studies have found the opposite (38,46). In our study, age and gender did not show a significant relationship with the occurrence of DVT.

The present investigation is the first looking into how the periodic variance in pneumonia's CT severity affects the likelihood of developing DVT. In our study, we found that the risk of DVT is high in patients with severe pneumonia at the time of admission. However, patients with a low pneumonia severity score on the first CT and a high CT-SS on the consecutive second and/or third CT did not have an increased risk of DVT. This showed us an increased risk of DVT in COVID-19 patients who had severe pneumonia at the time of diagnosis.

The present research has some limitations. First, the current study is retrospective, whereas multicenter prospective trials are required. Second, all patients have applied the lower extremity CDUS. However, only the patients with PE suspicion were taken to CTPA. Since CTPA was not performed in all patients, the incidence of PE could not be optimally evaluated.

In conclusion, since the risk of lower extremity DVT may be higher in COVID-19 patients with intense lung involvement on chest CT taken at the time of admission, it is important to start prophylactic anticoagulant treatment in these patients.

Conflict of interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

REFERENCES

1. Zhang J, Meng G, Li W, et al. Relationship of chest CT score with clinical characteristics of 108 patients hospitalized with COVID-19 in Wuhan, China. Respir Res. 2020;21(1):180.
2. Ding X, Xu J, Zhou J, Long Q. Chest CT findings of COVID-19 pneumonia by duration of symptoms. Eur J Radiol. 2020;127:109009.
3. Pan F, Ye T, Sun P, et al. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). Radiology. 2020;295(3):715-721.
4. Iba T, Levy JH, Connors JM, Warkentin TE, Thachil J, Levi M. The unique characteristics of COVID-19 coagulopathy. Crit Care. 2020;24(1):360.
5. Rauch A, Dupont A, Goutay J, et al. Endotheliopathy Is Induced by Plasma From Critically Ill Patients and Associated With Organ Failure in Severe COVID-19. Circulation. 2020;142(19):1881-4.
6. Voicu S, Delrue M, Chousterman BG, et al. Imbalance between procoagulant factors and natural coagulation inhibitors contributes to hypercoagulability in the critically ill COVID-19 patient: clinical implications. Eur Rev Med Pharmacol Sci. 2020;24(17):9161-8.
7. Salabei JK, Fishman TJ, Asnake ZT, Ali A, Iyer UG. COVID-19 Coagulopathy: Current knowledge and guidelines on anticoagulation. Heart Lung. 2021;50(2):357-60.
8. Wu MA, Colombo R, Arquati M, et al. Clinical-radiological correlations in COVID-19-related venous thromboembolism: Preliminary results from a multidisciplinary study. Int J Clin Pract. 2021;75(9):e14370.
9. Thomas MR, Scully M. Clinical features of thrombosis and bleeding in COVID-19. Blood. 2022;140(3):184-95.
10. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475–81.
11. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020;191:145-7.
12. Goeijenbier M, van Wissen M, van de Weg C, et al. Review: Viral infections and mechanisms of thrombosis and bleeding. J Med Virol. 2012;84(10):1680-96.
13. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med. 2020;58(7):1116-20.
14. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. Am J Hematol. 2020;95(7):834-47.
15. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost. 2020;18(6):1421-4.
16. Trigonis RA, Holt DB, Yuan R, et al. Incidence of Venous Thromboembolism in Critically Ill Coronavirus Disease 2019 Patients Receiving Prophylactic Anticoagulation. Crit Care Med. 2020;48(9):e805-8.
17. Léonard-Lorant I, Delabranche X, Séverac F, et al. Acute Pulmonary Embolism in Patients with COVID-19 at CT Angiography and Relationship to d-Dimer Levels. Radiology. 2020;296(3):E189-91.
18. Needleman L, Cronan JJ, Lilly MP, et al. Ultrasound for Lower Extremity Deep Venous Thrombosis: Multidisciplinary Recommendations From the Society of Radiologists in Ultrasound Consensus Conference. Circulation. 2018;137(14):1505-15.
19. Li JY, Wang HF, Yin P, et al. Clinical characteristics and

risk factors for symptomatic venous thromboembolism in hospitalized COVID-19 patients: A multicenter retrospective study. J Thromb Haemost. 2021;19(4):1038-48.
20. Elmokadem AH, Mounir AM, Ramadan ZA, Elsedeiq M, Saleh GA. Comparison of chest CT severity scoring systems for COVID-19. Eur Radiol. 2022;32(5):3501-12.
21. Cronan JJ, Dorfman GS, Scola FH, Schepps B, Alexander J. Deep venous thrombosis: US assessment using vein compression. Radiology. 1987;162(1 Pt 1):191-4.
22. The Lancet Haematology. COVID-19 coagulopathy: an evolving story. Lancet Haematol. 2020;7(6):e425.
23. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75(23):2950-73.
24. Zhai Z, Li C, Chen Y, et al. Prevention and Treatment of Venous Thromboembolism Associated with Coronavirus Disease 2019 Infection: A Consensus Statement before Guidelines. Thromb Haemost. 2020;120(6):937-48.
25. Suh YJ, Hong H, Ohana M, et al. Pulmonary Embolism and Deep Vein Thrombosis in COVID-19: A Systematic Review and Meta-Analysis. Radiology. 2021;298(2):E70-80.
26. Voicu S, Bonnin P, Malissin I, et al. Characteristics of deep vein thrombosis in the critically ill COVID-19 patient - an observational cohort study with Doppler ultrasound measurements. Eur Rev Med Pharmacol Sci. 2022;26(2):686-94.
27. Goldhaber SZ, Piazza G. Pulmonary Embolism and Deep Vein Thrombosis. Cardiovasc Ther A Companion to Braunwald's Hear Dis Fourth Ed. 2012;19(5):580–95.
28. Jiménez D, García-Sanchez A, Rali P, et al. Incidence of VTE and Bleeding Among Hospitalized Patients With Coronavirus Disease 2019: A Systematic Review and Meta-analysis. Chest. 2021;159(3):1182-96.
29. Edler C, Schröder AS, Aepfelbacher M, et al. Dying with SARS-CoV-2 infection-an autopsy study of the first consecutive 80 cases in Hamburg, Germany. Int J Legal Med. 2020;134(4):1275-1284.
30. Zhou S, Chen C, Hu Y, Lv W, Ai T, Xia L. Chest CT imaging features and severity scores as biomarkers for prognostic prediction in patients with COVID-19. Ann Transl Med. 2020;8(21):1449.
31. Francone M, Iafrate F, Masci GM, et al. Chest CT score in COVID-19 patients: correlation with disease severity and short-term prognosis. Eur Radiol. 2020;30(12):6808-17.
32. Espallargas I, Rodríguez Sevilla JJ, Rodríguez Chiaradía DA, et al. CT imaging of pulmonary embolism in patients with COVID-19 pneumonia: a retrospective analysis. Eur Radiol. 2021;31(4):1915-22.
33. Fang C, Garzillo G, Batohi B, et al. Extent of pulmonary thromboembolic disease in patients with COVID-19 on CT: relationship with pulmonary parenchymal disease. Clin Radiol. 2020;75(10):780-8.
34. Yu Y, Tu J, Lei B, et al. Incidence and Risk Factors of Deep Vein Thrombosis in Hospitalized COVID-19 Patients. Clin Appl Thromb Hemost. 2020;26:1076029620953217.
35. Dujardin RWG, Hilderink BN, Haksteen WE, et al. Biomarkers for the prediction of venous thromboembolism in critically ill COVID-19 patients. Thromb Res. 2020;196:308-12.
36. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020;18(8):1995-2002.
37. Barnes GD, Burnett A, Allen A, et al. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. J Thromb Thrombolysis. 2020;50(1):72-81.
38. Kirshblum SC, DeLauter G, Eren F, et al. Screening for Deep Vein Thrombosis in Persons With COVID-19 Upon Admission to an Inpatient Rehabilitation Hospital. Am J Phys Med Rehabil. 2021;100(5):419-23.
39. Ahuja N, Bhinder J, Nguyen J, et al. Venous thromboembolism in patients with COVID-19 infection: risk factors, prevention, and management. Semin Vasc Surg. 2021;34(3):101-16.
40. Lippi G, Favaloro EJ. D-dimer is Associated with Severity of Coronavirus Disease 2019: A Pooled Analysis. Thromb Haemost. 2020;120(5):876-8.
41. Thondapu V, Montes D, Rosovsky R, et al. Venous thrombosis, thromboembolism, biomarkers of inflammation, and coagulation in coronavirus disease 2019. J Vasc Surg Venous Lymphat Disord. 2021;9(4):835-44.
42. Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood. 2020;136(4):489-500.
43. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18(5):1094-9.
44. Zhou Y, Yang Q, Chi J, et al. Comorbidities and the risk of severe or fatal outcomes associated with coronavirus disease 2019: A systematic review and meta-analysis. Int J Infect Dis. 2020;99:47-56.

45. Xiong X, Chi J, Gao Q. Prevalence and risk factors of thrombotic events on patients with COVID-19: a systematic review and meta-analysis. Thromb J. 2021;19(1):32.
46. Koleilat I, Galen B, Choinski K, et al. Clinical characteristics of acute lower extremity deep venous thrombosis diagnosed by duplex in patients hospitalized for coronavirus disease 2019. J Vasc Surg Venous Lymphat Disord. 2021;9(1):36-46.
47. Chang H, Rockman CB, Jacobowitz GR, et al. Deep vein thrombosis in hospitalized patients with coronavirus disease 2019. J Vasc Surg Venous Lymphat Disord. 2021;9(3):597-604.