ORIGINAL ARTICLE

Investigation of Thromboembolic Events in COVID-19 Infected Patients

COVID-19 Enfekte Hastalarda Tromboembolik Olayların Araştırılması

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ABSTRACT

Aim: The objective of this study was to determine the patient characteristics and clinical outcomes of COVID-19 patients who experienced a thromboembolic event (TEE) and the frequency of this complication.

Materials and Methods: Between January 2020 and December 2021, all the patients with positive COVID-19 PCR test results were enrolled in this study. The data of the cases that developed TEE with the diagnosis of COVID-19 were evaluated retrospectively.

Results: During the study period, a total of 2,845 patients were hospitalized with a diagnosis of COVID-19. Among this group, 96 patients (3.37%) had TEE associated with COVID-19. The mean age was 63.76 ±13.85 years (range: 28-80 years), with 46 males (4.92%) and 50 females (52.08%). Of these patients, 46 (47.92%) had severe COVID-19 and 50 (52.08%) had only mild respiratory symptoms. Patients in the severe COVID-19 group were older, but there was no statistical significance between the groups. The peripheral venous disease was more common in the mild COVID-19 group while the peripheral arterial disease was more common in the severe COVID-19 group. CRP, uric acid, troponin, creatinine, D-dimer, and leukocyte levels were higher in severe COVID-19 patients with TEE (p<0.05). 81 of 96 patients (84.37%) had the peripheral venous disease, 5 of 96 patients (5.2%) had peripheral arterial disease and 11 of 96 patients (11.45%) had a pulmonary embolism. One patient (1.04%) had both peripheral venous disease and pulmonary embolism. The overall mortality rate was 6.25% (6/96).

Conclusions: The thrombotic process associated with COVID-19 affects venous structures more frequently than arteries. Given the significant risk observed for TEE in COVID-19, diagnostic imaging for TEE should be considered with a high degree of clinical suspicion.

Keywords: COVID-19; SARS-CoV-2; Thrombosis; Embolism

ÖZ

Aim: Bu çalışmadaki amaç tromboembolik olay (TEE) yaşayan COVID-19 hastalarının hasta özelliklerini ve klinik sonuçlarını ve bu komplikasyonun sıklığını belirlemekti.

Gereç ve Yöntemler: Ocak 2020 ve Aralık 2021 tarihleri arasında COVID-19 PCR test sonuçları pozitif olan tüm hastalar bu çalışmaya dahil edildi. COVID-19 tanısı ile TEE gelişen vakaların verileri retrospektif olarak değerlendirildi.

Bulgular: Çalışma dönemi boyunca toplam 2.845 hasta COVID-19 tanısı ile yatarak tedavi görmüştü. Bu grup içinde 96 hastada (%3,37) COVID-19 ile ilişkili TEE vardı. Ortalama yaş 63,76 13,85 yıl (aralık: 28-80 yıl) olup, bu olguların 46 erkek (%4,92) ve 50 kadın (%52,08) idi. Bu hastalardan 96'sının 46'sında (%47,92) şiddetli COVID-19 vardı ve 96'sının 50'sinde (%52,08) sadece hafif solunum semptomları vardı. Şiddetli COVID-19 grubu hastaları daha yaşlıydı, ancak gruplar arasında istatistiksel anlamlılık yoktu. Periferik venöz hastalık hafif COVID-19 grubunda daha yaygınken, periferik arter hastalığı şiddetli COVID-19 grubunda daha yaygın olarak saptandı. CRP, ürik asit, troponin, kreatinin, D-dimer ve lökosit seviyeleri TEE'si olan ağır COVID-19 hastalarında daha yüksekti (p<0,05). 96 hastanın 81'inde (%84,37) periferik venöz hastalık, 96 hastanın 5'inde (%5,2) periferik arter hastalığı ve 11'inde (%11,45) pulmoner emboli mevcuttu. Bir hastada (%1,04) hem periferik venöz hastalık hem de pulmoner emboli vardı. Genel mortalite oranı %6,25 (6/96) idi.

Sonuçlar: COVID-19 ile ilişkili trombotik süreç venöz yapıları arterlerden daha sık etkilemektedir. COVID-19'da TEE için gözlenen önemli risk göz önüne alındığında, TEE için tanısal görüntüleme yüksek derecede klinik şüphe ile değerlendirilmelidir.

Anahtar Kelimeler: COVID-19; SARS-CoV-2; Tromboz; Emboli

Introduction

Coronavirus Disease of 2019 (COVID-19) is a viral infection caused by the SARS-CoV-2 coronavirus (Severe Acute Respiratory Syndrome Coronavirus 2) and causes mainly respiratory symptoms. Although COVID-19 was previously believed to cause only respiratory illness, it was soon realized that many organ systems might also be damaged (1). This infection has been reported to enhance the incidence of venous and arterial TEE despite being a respiratory condition. The general scientific community is paying attention to the connection between COVID-19 and thrombosis (2,3). A strong inflammatory response that triggers a widespread hypercoagulable condition has been hypothesized as the cause of this situation (4). According to the initial research on COVID-19 coagulopathy, sepsis-induced cytokine release, an increase in Angiotensin II, a reduction in vasodilator angiotensin, and a combination of these factors led to a hypercoagulable condition (5). According to various hypotheses, elevated autoimmune antibodies could trigger an inflammatory state that increases the risk of thrombosis (6). Venous thromboembolism (VTE), which affects 20% of these patients and occurs more frequently in those who are critically ill, is thought to be related to

a considerable risk for COVID-19 (7-10). But there is a shortage of data about Turkish COVID-19 patients. Our study's objectives were to examine the prevalence of TEE in COVID-19 patients receiving hospital care at our hospital, as well as to reveal the patient characteristics and clinical outcomes of those who experience this complication.

Materials and Methods

Between January 2020 and December 2021, hospitalized patients with positive COVID-19 PCR test results were included in this study at one center's COVID-19 wards and intensive care unit (ICU). The study was approved by the Ministry of Health's COVID-19 Scientific Research Assessment Commission and the university faculty of the medical ethics committee (decision number, 2022-03, date: 02.02.2022).

Hospitalized patients who were over 18 years old and whose combined nasopharyngeal swab sample tests were positive for COVID-19 polymerase chain reaction (PCR) (as determined by the microbiology laboratory at our hospital) were the subjects of the study. The study was carried out retrospectively, and the hospital automation system (MIA-med) was used to retrieve the information about these patients. Patients with negative COVID-19 PCR test results at one center but with positive COVID-19 PCR test results at another medical facility were excluded from the research.

According to information from the World Health Organization and the Ministry of Health's COVID-19 Diagnosis and Treatment Guideline, the cases' diagnoses, treatments, and follow-ups were organized. According to the Ministry of Health of the Republic of Turkiye, patients with COVID-19 were categorized as severe disease and mild disease. The data pertain to cases and include epidemiological and demographic information, age, gender, contact and transmission history, the presence of concomitant chronic disease and risk factors, symptoms, and signs, as well as laboratory and radiological findings (hemogram, c reactive protein (CRP), procalcitonin, erythrocyte sedimentation rate (ESR), alanine aminotransferase (ALT) aspartate aminotransferase (AST), urea, creatinine, Lactate Dehydrogenase (LDH) triglyceride, D-dimer, international normalized ratio (INR), ferritin. Chest radiography, chest CT (computed tomography), arterial and venous doppler ultrasonography results were analyzed.

The Turkish Ministry of Health's COVID-19 guidelines were used to classify the severity of the disease.

Statistical analysis

SPSS 19.0 (SPSS INC, Chicago, Il, USA) application was obtained by using statistical data. Kolmogorov - Smirnov test was used to assess the continuous distribution of variables. The continuous variables obtained as a result of the analysis are expressed as mean ± standard deviation. T-tests and Mann-Whitney tests were used in the comparison of parameters that

fit and do not comply with the normal distribution. 95 % confidence intervals were calculated with standardized beta coefficients. The p value < 0.05 was considered statistically significant.

Results

During the study period, 2.845 inpatients were admitted with COVID-19. Among this group, 96 patients (3.37%) had TEE associated with COVID-19. The mean age was 63.76±13.85 years (range, 28–80 years) with 46 men (47.92%) and 50 women (52.08%). The peripheral venous disease was present in 81 of 96 (84.37%), peripheral arterial disease in 5 of 96 (5.2%), and pulmonary embolism in 11 (11.45%) cases (Figure 1).

Of the patients, 46 of 96 (47.92%) had severe COVID-19, and 50 of 96 (52.08%) had only mild respiratory symptoms. The distribution of ischemic events: One (1.04%) patient had both cerebral and lower extremities while three (3.12%) patients had at least one lower limb ischemia. Four patients had revascularization attempts, and three of them (or 75%) were able to save a limb. The overall mortality was 6.25% (6/96). The most prevalent underlying disease were diabetes mellitus (22.91%) and history of smoking (35.41%). Table 1 summarizes the characteristics of the COVID-19 patients with TEE.

CRP, uric acid, troponin, creatinine, D-dimer, and leukocyte levels were higher in severe COVID-19 patients with TEE (p<0.05). Also, the severe COVID-19 group patients were older but there was no statistical significance between the groups (Table 2).

The mean troponin levels were higher in the male group (Figure 2).

The peripheral venous disease was more common in the mild COVID-19 group, while the peripheral arterial disease is more common in the severe COVID-19 group (Table 3).
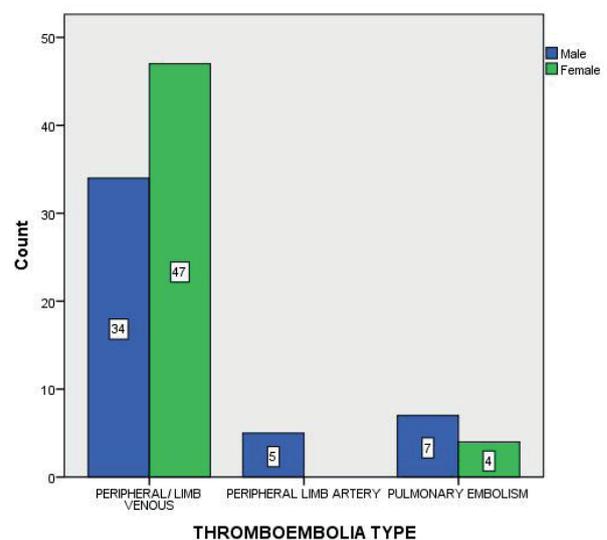

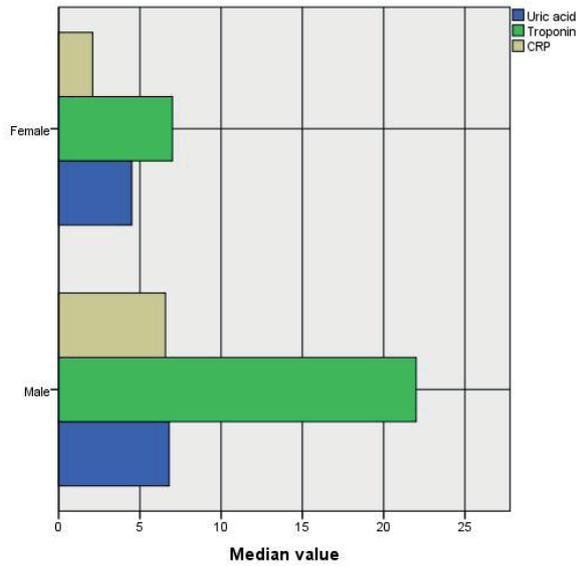**Figure 1.** Distribution of thromboembolism types between genders

Figure 2. Figure showing the median value of uric acid, crp, and troponin between the genders.

Table 1. Characteristics of the COVID-19 patients with thromboembolic events

	COVID-19 patients with thromboembolic event (n=96)
Age (years)	63.76±13.85
Gender (male)	46 (47.92%)
Diabetes mellitus	22 (22.91%)
Hypertension	10 (10.4%)
Coronary artery disease	5 (5.2%)
Chronic kidney disease/end-stage renal disease	11 (11.45%)
Smoking history	34 (35.41%)
Hyperlipidemia	16 (16.66%)
Atrial fibrillation	3 (3.12%)
Obesity (BMI>30)	10 (10.4%)
Pre-COVID-19 prophylactic anticoagulation	5 (5.2%)
Glucose (mg/dl)	111 (97-152.5)
Creatinine (mg/dl)	0.93 (0.8-1.32)
Uric acid	5.6 (3.9-7.1)
Sodium (mmol/L)	138 (135-140)
Potassium (mmol/L)	4.2 (3.9-4.5)
AST (U/L)	30 (20.5-41)
ALT (U/L)	21 (14-36.5)
Hgb (g/dl)	12.50±2.25
WBC count,10⁹/ L	8.05±5.67
Platelet count 10⁹/ L	196 (156-235)
RDW (%)	14.46±1.97
CRP	2.68 (0.86-10)
D-dimer	1.78 (0.34-2.95)
Troponin ng/L	9 (5-29)

*BMI: Body mass index

Table 2. Laboratory characteristics between genders of COVID-19 patients with thromboembolic events

Characteristics	Severe COVID-19 (n= 46)	Mild COVID-19 (n=50)	p value
Age (years)	66.34±14.32	61.38±13.09	0.790
Glucose (mg/dl)	120 (98-155)	105.5 (97-105.5)	0.684
Creatinine (mg/dl)	1.09 (0.85-1.71)	0.84 (0.72-0.84)	<0.001
Uric acid	6.7 (5.6-8.1)	4.5 (3.4-4.5)	<0.001
Sodium (mmol/L)	137 (135-139.5)	138 (134.2-138)	0.659
Potassium (mmol/L)	4.3 (3.8-4.7)	4.08 (3.9-4.5)	0.246
AST (U/L)	34 (20-43)	29 (20.5-29)	0.201
ALT (U/L)	24 (14.5-41)	20 (13.2-31)	0.237
Hgb (g/dl)	12.78±2.52	12.26±1.96	0.255
Leukocyte count,10⁹/ L	9.65±6.31	6.61±4.85	0.008
Platelet count 10⁹/ L	196 (156.5-251.5)	196 (154.5-233.2)	0.851
RDW (%)	14.42±1.79	14.51±2.15	0.828
CRP	6.43 (1.36-14)	1.9 (0.4-3.72)	<0.001
D-dimer	1.77 (0.38-2.95)	0.77 (0.34-1.3)	<0.001
Troponin ng/L	22 (8-45.5)	7 (3-15.5)	<0.001

Table 3. Distubition of thromboembolic event's form according to disease severity

Thromboembolic event's form	Severe COVID-19 (n= 46)	Mild COVID-19 (n=50)	Total
Peripheral venous disease	33	48	81
Peripheral arterial disease	5	0	5
Pulmonary embolism	8	3	11
Both peripheral venous disease and pulmonary embolism	1	0	1

Discussion

Numerous observational research has revealed that patients with COVID-19 both hospitalized in wards and ICUs experienced unusually high rates of VTE. Many of these previous studies showed significant rates of VTE even when patients were receiving routine or even stronger pharmacologic prophylaxis for the condition. Acute respiratory distress syndrome patients have also received fibrinolytic treatment in some studies. Unfortunately, there are not enough high-quality randomized controlled trials (11).According to a recent study, the incidence rate of TEE among hospitalized COVID-19 patients ranges from 2.6 to 85% (both mild or severe COVID-19-infected patients) (12). Although it is difficult to determine the exact incidence of COVID-19-related TEE, it seemed to be low (3.37%) in our center during the COVID-19 pandemic. Because it only includes severe instances required consultation with vascular surgery, the published number, which was based on a voluntary survey of physicians, probably underestimates the true incidence. There is a close association between COVID-19 and VTE. Its connection to VTE is becoming clear as our knowledge grows. The incidence of VTE in COVID-19 individuals

differs between the studies that were described in the literature. VTE is generally more frequently seen in patients in ICU and in cases of severe disease. On the other hand, the literature is inconsistent when it comes to the use of anticoagulant prophylaxis (12). We found that COVID-19 VTE affected 3,37% of the inpatients. As would typically happen with ischemia brought on by atherosclerosis, the younger age groups were not spared by the age spectrum. Indes et al. (13) reported that the patients who tested positive for SARS-CoV-2 and had arterial thrombosis evidence tended to be younger and more often male. However, we did not include patients in our study who had negative COVID-19 PCR test results. In our study, both arterial and venous thromboembolism cases were included and there was no significant difference according to gender. Since the number of cases with arterial involvement was insufficient, we could not make a comparison between the groups. The goal of the study was to determine the common traits of individuals who experienced a COVID-19-related TEE.

Compared to hemorrhagic coagulopathy, COVID-19-induced coagulopathy (CIC) appears to be more prothrombotic. The idea that CIC may represent an unrestrained immunothrombotic reaction to COVID-19 is supported by mounting data on venous and arterial TEE in these critically ill COVID-19 patients. It has been suggested that hypoxia, a significant inflammatory response, a severe illness, and underlying risk factors may also make patients more vulnerable to TEEs (13-18). However, there were 46 TEE in the severe COVID-19 group and 50 in the mild COVID-19 group in the present study.

Patients who are hospitalized and have an acute medical condition, like an infection, are more likely to develop VTE. Depending on the method of measurement, the percentage of VTE in patients in general wards ranges from 5% to 15%. Pharmacologic prophylaxis is used to reduce the risk to 2.8% 5%. The risk of VTE increases in patients in the ICU (11). One meta-analysis found rates ranging from 10% to 30% (18). The rate of VTE in hospitalized wards and ICU patients with COVID-19 has been observed in several studies to be higher than anticipated (19-26).In our study, even though ICU patients were included, we divided the groups into mild and severe. Peripheral venous disease was more common in the mild COVID-19 group, while peripheral arterial disease is more common in the severe COVID-19 group. Since there have been no placebo-controlled randomized trials, it is impossible to determine the true risk of VTE in COVID-19 patients. According to reports, rates of VTE in general medical ward patients with COVID-19 range from about 4% in patients who underwent a clinical evaluation to as high as 15% in those who underwent compression ultrasound screening (25,27,28). Arterial/venous Doppler or thoracic CT angiography was not performed on all covid 19 patients in our series. The patients included in the study due to thromboembolism were the patients who were consulted and diagnosed

with TEE. Some patients may have been overlooked.

In conclusion, the TEEs associated with COVID-19 affect venous structures more frequently than arteries. Given the significant risk observed for TEE in COVID-19, caution should be exercised for this potentially mortal complication. Although the rate of TEE seems to be relatively low in our study, some patients may have been missed in our retrospective study. COVID-19 patients should be evaluated for TEE and further investigations, including imaging, should be performed in the presence of high clinical suspicion.

Limitations

This study had a retrospective and,a single-center design and also did not include a control group. The small sample size limits the statistical significance of our findings. Due to the relatively low rates of COVID-19-associated arterial thrombosis, it is doubtful that any significant numbers will be reported. Smaller detailed reports, like ours, will therefore be useful to comprehend the general course of the disease.

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