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In-Hospital Clinical Outcomes of Covid-19 Patients Treated with Oral Anticoagulants

Oral Antikoagülan Kullanan Covid-19 Hastalarının Hastane İçi Klinik Sonuçları

[1]Salih ŞAHİNKUŞ, [2]Selçuk YAYLACI

[1]Cardiology Department, Sakarya University Education and Research Hospital, Sakarya, Türkiye
[2]Internal Medicine Department, Medical Faculty of Sakarya University, and Education and Research Hospital, Sakarya, Türkiye

Salih Şahinkuş: https://orcid.org/0000-0003-1558-5761
Selçuk Yaylaci: https://orcid.org/0000-0002-6768-7973

ABSTRACT

Objective: We aimed to investigate the effects of warfarin and new-generation oral anticoagulants on the prognosis of patients diagnosed with coronavirus disease 2019 (COVID -19).

Materials and Methods: Patients diagnosed with COVID -19 were divided into two groups depending on whether they were using warfarin or a new-generation oral anticoagulant. The types of chronic diseases, drugs used, hematological and biochemical parameters, and prognoses in each group were statistically analysed.

Results: Twenty-three patients (37.1%) using warfarin and 39 (62.9%) patients using new-generation oral anticoagulants were included in the study. There was no significant difference between the two groups regarding demographic characteristics and laboratory data. The mortality rates for the warfarin and new-generation anticoagulant groups were similar (39.1% vs. 43.6%, respectively; p = 0.731). Also, there was no significant difference in the results of major bleeding and intubation rates between the two groups.

Conclusion: There was no difference in the effects of warfarin and new-generation oral anticoagulants on mortality, intubation and major bleeding among the patients with COVID-19.

Keywords: Anticoagulation, coronavirus, Covid-19, thrombosis

ÖZ

Amaç: Çalışmamızda varfarin ve yeni nesil oral antikoagülanların COVID-19 hastalığının prognozu üzerine etkilerini araştırmayı amaçladık.

Materyal ve Metot: COVID-19 tanısı alan hastalar, varfarin veya yeni nesil oral antikoagülan kullanıp kullanmamalarına göre iki gruba ayrıldı. Her gruptaki kronik hastalık tipleri, kullanılan ilaçlar, hematolojik ve biyokimyasal parametreler ve prognozlar istatistiksel olarak analiz edildi.

Bulgular: Varfarin kullanan 23 (%37,1) hasta ve yeni nesil oral antikoagülan kullanan 39 (%62,9) hasta çalışmaya dahil edildi. Her iki grup arasında demografik özellikler ve laboratuvar verileri açısından anlamlı fark yoktu. Varfarin ve yeni nesil antikoagülan gruplarında mortalite oranları benzerdi (sırasıyla %39,1 ve %43,6; p = 0,731). Ayrıca majör kanama ve entübasyon oranları sonuçlarında da iki grup arasında anlamlı fark yoktu.

Sonuç: COVID-19 hastalarında varfarin ve yeni nesil oral antikoagülanların entübasyon, majör kanama ve mortalite üzerine etkileri arasında fark yoktu.

Anahtar Kelimeler: Antikoagülasyon, Covid-19, koronavirüs, tromboz

Sorumlu Yazar / Corresponding Author:
Salih Şahinkuş
Adnan Menderes road, Saglik street, Sakarya University Education and Research Hospital, Sakarya, Türkiye
Tel: +90-505-779-2642
Fax: +90-312-319-8236
E-mail: canerbaysan@gmail.com

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) virus, or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an RNA virus. Infection with this virus can lead to a wide range of symptoms, from mild to lung infection with severe respiratory failure.[1] COVID-19 has been classified as a pandemic by the World Health Organization.[2] Patients with COVID-19 may be asymptomatic; however, the disease may also present with symptoms such as fever, chills, cough, shortness of breath, myalgia, and headache. The case fatality rate is 2%–3%. The laboratory tests for COVID-19 are nonspecific and include creatine kinase, lactate dehydrogenase, D-dimer (a specific fibrin degradation product), hemogram, white blood cell count, serum C-reactive protein (CRP), sedimentation rate and procalcitonin. Low lymphocytes and platelets can be seen in COVID-19 patients. Pathological changes in these parameters are also used as prognostic factors.[3]

Since the COVID-19 pandemic is new, copious studies about the characteristics and treatment of the virus and the disease are being added to the literature. However, despite many new scientific studies in the literature daily, there needs to be more sufficient and definitive information about COVID-19 and its treatment. Although it is emphasised that impaired coagulation parameters are associated with a poor prognosis in COVID-19,[4] there are limited data in the literature on warfarin, new-generation oral anticoagulants (NOAC) and low-molecular-weight heparin treatments for the disease.[5]

In this study, we aimed to investigate the effects of warfarin and NOAC use on the prognosis of patients diagnosed with COVID-19.

MATERIALS AND METHODS

Ethical Statement: Approval for this study was obtained from the ethics committee of Sakarya University, Faculty of Medicine (Date: 27/04/2020, decision no: 71522473/050.01.04/463). The study was carried out following the international declaration, guidelines, etc.

Patients: Sixty-two patients diagnosed with COVID -19, treated in intensive care, and followed up in our hospital were included in the study. Following ethics committee approval, the patient's data were collected retrospectively through the electronic medical records. Clinical findings, laboratory parameters, computed tomography and SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) were used to diagnose the patients with COVID-19. The patients were divided into two groups depending on the use of either warfarin or NOACs. The NOACs used were apixaban, rivaroxaban, dabigatran and edoxaban. The types of chronic diseases, drugs used, hematological and biochemical parameters and prognoses in each group were statistically analysed.

Sample Collection, Nucleic Acid Isolation and RT-PCR Reactions: Combined nasopharynx and oropharynx swab samples were taken with a Dacron swab, placed in a viral transport medium, and immediately transported to the laboratory at 2ºC–8ºC. The samples were sent to the laboratory following the cold chain rules using the triple transport system and following infection prevention and control procedures. After the samples had been accepted in the microbiology laboratory, they were taken to a third-level biosecurity negative pressure room. The Bio-Speedy® Viral Nucleic Acid Isolation Kit was used to isolate total nucleic acid from samples (Bioeks, İstanbul, Turkey). The isolation procedure was carried out in line with the manufacturer's recommendations. The Bio-Speedy® Covidien work for RT-PCR Detection Kit-19 RT-qPCR (Bioeks, İstanbul, Turkey) was used. The manufacturer's recommendations carried out PCR amplification and the evaluated the results.

Statistical Analysis: Descriptive analyses were performed to provide information on the general characteristics of the study population. Visual (i.e., probability plots, histograms) and analytical (Kolmogorov–Smirnov test, Shapiro–Wilk test) methods were used to determine whether the data were normally distributed. The descriptive analyses were presented using medians and interquartile ranges for the non-normally distributed variables. The Mann–Whitney *U* test was used for the nonparametric tests to compare these parameters. Pearson's chi-square test was used to compare the categorical variables between the two groups. The categorical variables were presented as the frequency (% percentage). A p-value <0.05 was considered statistically significant. The analyses were performed using SPSS Statistics version 22.0 (IBM Corporation, Armonk, NY).

RESULTS

When the demographic characteristics of the patients were compared, no significant differences were found between the two groups other than the use of insulin and alpha-blocker therapy. While all the patients using NOAC were taking the drug due to atrial fibrillation (AF), 19 of the patients using warfarin were using it because of AF, and four had a prosthetic heart valve (Table 1).

Table 1. Comparison of baseline characteristics and the drug they use of the warfarin and NOAC groups.

		Warfarin, n = 23 (37.1%)	NOAC, n = 39 (62.9%)	p
Sex, n (%)		Female, n = 11 (47.8) Male, n = 12 (52.2)	Female, n = 16 (41.0) Male, n = 23 (59.0)	0.602
Hypertension, n (%)		18 (78.3)	27 (69.2)	0.441
Diabetes Mellitus, n (%)		11 (47.8)	12 (30,8)	0.179
CAD history, n (%)		3 (13.0)	9 (23.1)	0.323
CVD history, n (%)		8 (34.8)	6 (15.4)	0.078
PAD history, n (%)		0 (0.0)	2 (5,1)	0.526
COPD history, n (%)		3 (13.0)	10 (25.6)	0.338
CKD, n (%)		3 (13.0)	6 (15,4)	0.928
Hyperlipidemia, n (%)		3 (13.0)	8 (30,5)	0.516
CHF, n (%)		4 (17.4)	7 (17.9)	0.978
DRUGS (Already taken)	ACE/ARB, n (%)	14 (60.6)	24 (61.5)	0,998
	CCBs, n (%)	10 (43.5)	14 (35.9)	0.597
	Diuretics, n (%)	18 (78.3)	26 (66.7)	0.331
	Beta blockers, n (%)	13 (56.5)	27 (69.2)	0.312
	Digoxin, n (%)	4 (17.4)	9 (23.1)	0.751
	Alfa blockers, n (%)	0 (0.0)	8 (20.5)	**0.021**
	Antiplatelet agent, n (%)	9 (39.1)	14 (35.9)	0.799
	OAD, n (%)	6 (26.1)	7 (17.9)	0.447
	Insülin, n (%)	5 (21.7)	0 (0.0)	**0.005**
	Bronchodilators, n (%)	2 (8.7)	5 (12.8)	0.620
	Statins, n (%)	3 (13.0)	6 (15.4)	0.770
	MRA, n (%)	5 (21.7)	7 (17.9)	0.715

CAD: Coronary Artery Disease; CVD: Cerebrovascular Disease; PAD: Peripheral Artery Disease; COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease; CHF: Congestive Heart Failure; ACE: Angiotensin-converting Enzyme; ARB: Angiotensin Receptor Blocker; CCB: Calcium Channel Blocker; OAD: Oral Antidiabetic; MRA: Mineralocorticoid Receptor Antagonist.

When the laboratory values of the patients in the two groups were compared, no differences were found except that the prothrombin time and international normalised ratio (PT-INR) values were higher in the warfarin group (Table 2).

Table 2. Comparison of laboratory test results of the two groups.

	Warfarin, n = 23	NOAC, n = 39	p
WBC count, kU/l	9.6 ± 5.8	11.3 ± 6.7	0.453
Hemoglobin, g/dL	10.5 ± 3.2	11.6 ± 2.2	0.170
Hematocrit, %	35.1 ± 8.5	37.5 ± 7.2	0.407
Lymphocyte 10^3/uL	1.2 ± 0.5	1.3 ± 1.4	0.839
Neutrophile, 10^3/uL	8.0 ± 5.7	9.2 ± 6.0	0.429
Platelet, 10^3/uL	199 ± 93	206 ± 88	0.829
Prothrombin time, seconds	40.4 ± 31.3	15.2 ± 40.7	**0.001**
APTT, seconds	51.5 ± 42.4	32.8 ± 7.2	0.085
INR	3.9 ± 3.2	1.4 ± 0.4	**0.001**
D-DİMER, ng/mL	2661 ± 5595	1920 ± 1689	0.757
Hs-cTnI, ng/L	941 ± 3299	217 ± 787	0.759
Ferritin, ng/mL	675.5 ± 402.3	423.3 ± 387.3	0.400
Glucose, mg/dL	101.1 ± 93.1	104.2 ± 82.1	0.204
Urea, mg/dL	84.8 ± 23.6	94.9 ± 30.3	0.651
Creatinine, mg/dL	2.2 ± 2.4	1.4 ± 0.9	0.460
Albumin, g/dL	3.1 ± 0.4	3.2 ± 0.5	0.555
Lactate dehydrogenase, U/L	399.2 ± 85.3	349.5 ± 128.4	0.565
C reactive protein, mg/dL	68.8 ± 62.9	75.0 ± 95.1	0.257
Prokalsitonin, ng/mL	3.9 ± 3.5	10.8 ± 31	0.348
Sedimentation, mm/hour	65.4 ± 40.5	45.6 ± 28.7	0.129
Fibrinogen, g/L	400 ± 80	372 ± 95	0.431
CK-MB, IU/L	15.0 ± 4.1	25.2 ± 24.3	0.099
Lactate, mmol/L	2.9 ± 1.8	2.5 ± 1.7	0.427

WBC; White Blood Cell; APTT; Activated Partial Thromboplastin Time; INR; International Normalized Ratio; Hs-cTnI; High sensitive Cardiac Troponin I; CK-MB; Creatine Kinase Myocardial Band.

When the subgroup mortality analysis was performed, 14 of the 23 (37.0%) patients with diabetes (p = 0.020), 7 of the 9 (14.5%) patients with chronic renal failure (p = 0.018), and 3 of the 11 (17.7%) patients with heart failure (p = 0.003) died. These chronic diseases were statistically significant in terms of death among the COVID-19 patients. In the patients with exitus, the hemoglobin (10.2 ± 2.7 & 12 ± 2.3, respectively; p = 0.012) and hematocrit (34.3 ± 7.5 & 38 ± 7.7, respectively; p = 0.045) levels were lower compared to the patients who survived. Furthermore, these patients' CRP levels (103 ± 110 & 44 ± 54, respectively; p = 0.047), procalcitonin levels (16 ± 35 & 1 ± 2.5, respectively; p = 0.005), and sedimentation rates (62 ± 34 & 42 ± 23, respectively; p = 0.005) were significantly different from those who were discharged in good health (Table 2). In the warfarin group, only eight patients with INR were in the therapeutic range target value. The treatment of the patients with either warfarin or NOAC continued during their time in the ICU, and there was no difference between the two groups in terms of in-hospital mortality (Table 3).

Table 3. In-hospital clinical outcomes of the study groups.

	Warfarin,n = 23	NOAC n = 39	p
Intubation	3 (13.0)	10 (25.6)	0.338
Major Bleeding	0 (0.0)	2 (5.1)	0.526
Mortality n, (%)	9 (39.1)	17 (43.6)	0.731

DISCUSSION AND CONCLUSION

While COVID-19 can be asymptomatic, it can lead to flu-like symptoms, severe respiratory failure, multi-organ dysfunction and death.[3,6] Some laboratory parameters may also increase and decrease in the presence of COVID-19 infection depending on the pathogenesis of the disease. Low lymphocytes, albumin and platelets, and high CRP, procalcitonin, lactate dehydrogenase, creatinine, and D-dimer have been highlighted as poor prognostic factors.[1,3,7,8]

Thrombotic complications cause serious problems in patients who are positive for COVID-19.[9] As with viral infections, COVID-19 infection also activates coagulation and can cause the excessive activation of platelets. In addition, causing an inflammatory response systemically can affect the procoagulant and anticoagulant mechanisms in hemostasis and disrupt the balance between the two.[10,12] In autopsies of patients who died due to COVID-19, thrombus in the capillaries and small vessels and many microthrombi in the liver venous portal system were present.[13]

In severe COVID-19 cases, high D-dimer levels are encountered, revealing that they are associated with mortality. Again, these patients often have a coagulation disorder.[14]

In our study, the effects of warfarin and new-generation oral anticoagulants used to treat patients with COVID-19 were examined, and it was determined that there was no difference in the impact of these two groups of drugs on mortality. As expected, the PT-INR levels were significantly higher in the group using warfarin, but no significant difference was found in the other laboratory parameters.

In conclusion, based on the results of our study, neither warfarin nor NOACs were superior in treating patients with COVID-19 in terms of in-hospital clinical outcomes. The relatively low number of cases in this study was considered a limitation. Multicentre studies with more case numbers should be conducted to verify these results.

Ethics Committee Approval: Our study was approved by the Sakarya University Ethics Committee (Date: 27/04/2020, decision no: 71522473/050.01.04/463). The study was carried out following the international declaration, guidelines, etc.

Conflict of Interest: No conflict of interest was declared by the authors.

Author Contributions: Concept – SS, SY; Supervision – SS; Materials – SS, SY; Data Collection and/or Processing – SS, SY; Analysis and/or Interpretation – SS, SY; Writing –SS, SY.

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