Available online at **www. scholarsresearchlibrary.com**

Scholars Research Library

Der Pharmacia Lettre, 2021, 13 (5): 01-05
(http: //scholarsresearchlibrary. com/archive. html)

ISSN 0975-5071
USA CODEN: DPLEB4

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

Salih Sahinkus[1*], Ercan Aydin[2], Ahmet Cihad Genc[3], Selçuk Yaylaci[3]

[1]*Department of Cardiology, Sakarya University Education and Research Hospital, Sakarya, Turkey*
[2]*Department of Cardiology, Vakfikebir State Hospital, Trabzon, Turkey*
[3]*Department of Internal Medicine, Sakarya University Education and Research Hospital, Sakarya, Turkey*

[*]***Corresponding author:*** *Salih Sahinkus, Department of Cardiology, Sakarya University Education and Research Hospital, Sakarya, Turkey, Tel: +90 506 471 35 99; E-mail: drsalihsahinkus@gmail.com*

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, haematological 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 in terms of 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).

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

Keywords: COVID-19, SARS-cov-2, Thrombosis, Coagulopathy, Anticoagulants.

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 symptoms 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), haemogram, 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 very new, copious studies about the characteristics and treatment of the virus and the disease are being added to the literature. However, despite the fact that there are many new scientific studies in the literature from day to day, there is neither sufficient nor 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

Sixty-two patients who were diagnosed with COVID-19, treated in intensive care and followed up in our hospital were included in the study. The patients' data were collected retrospectively through the patient tracking system following ethics committee approval. 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, haematological and biochemical parameters and prognoses in each group were statistically analyzed.

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 in accordance with 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 for the isolation of total nucleic acid from samples (Bioeks, İstanbul, Turkey) was used. 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. PCR amplification and the evaluation of the results were carried out in accordance with the manufacturer's recommendations.

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 range 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).

Ethical approval

Approval for this study was obtained from the ethics committee of Sakarya University, Faculty of Medicine.

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 the drug because of AF, and four of them had a prosthetic heart valve (Table 1).

	Warfarin, n=23 (37.1%)	**NOAC, n=39 (62.9%)**	**p**
Sex, n (%)	**Female, n=11 (47.8)**	**Female, n=16 (41.0)**	**0,602**
	Male, n=12 (52.2)	**Male, n=23 (59.0)**	
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
Current malignancy, n (%)	0 (0.0)	0 (0.0)	
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)	0.62
Statins, n (%)	3 (13.0)	6 (15.4)	0.77
MRA, n (%)	5 (21.7)	7 (17.9)	0.715

Table 1: Comparison of baseline characteristics and the drugs they use of the warfarin and NOAC groups. **Abbreviations**: 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 normalized ratio (PT-INR) values were higher in the warfarin group (Table 2).

	Warfarin, n=23	**NOAC, n=39**	**p**
WBC count, kU/l	9.6 ± 5.8	11.3 ± 6.7	0.453
Hemoglobine, g/dL	10.5 ± 3.2	11.6 ± 2.2	0.17
Hematocrite, %	35.1 ± 8.5	37.5 ± 7.2	0.407
Lemphosite, 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
Platelete, 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	0.4
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	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

Table 2: Comparison of laboratory test results of the two groups. **Abbreviations**: 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.

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.

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, and these chronic diseases were statistically significant in terms of death among the COVID-19 patients. In the patients with exitus, the haemoglobin (10.2 ± 2.7 vs. 12 ± 2.3, respectively; p=0.012) and hematocrit (34.3 ± 7.5 vs. 38 ± 7.7, respectively; p=0.045) levels were lower compared to the patients who survived. Furthermore, these patients' CRP levels (103 ± 110 vs. 44 ± 54, respectively; p=0.047), procalcitonin levels (16 ± 35 vs. 1 ± 2.5, respectively; p=0.005) and sedimentation rates (62 ± 34 vs. 42 ± 23, respectively; p=0.005) were significantly different from those who were discharged in good health (Table 3).

	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

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

DISCUSSION

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 [1-8].

Thrombotic complications cause very 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, by causing an inflammatory response systemically, it can affect the procoagulant and anticoagulant mechanisms in haemostasis 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 micro thrombi in the liver venous portal system were found to be present [13].

In cases where COVID-19 is severe, 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 effects 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.

Based on the results of our study, neither warfarin nor NOACs were found to be superior in the treatment of 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 larger case numbers should be conducted to verify these results.

CONCLUSION

There was no difference in the effects of warfarin and new-generation oral anticoagulants on mortality among the patients with COVID-19.

CONFLICT OF INTEREST

All authors declare that there is no conflict of interest in this study.

REFERENCES

[1] Tian S, Hu N, Lou J, et al., *J Infect*, **2020**,80(4): 401-406.

[2] *World health organization*, **2020**.

[3] Madabhavi I, Sarkar M, Kadakol N., *Monaldi Arch Chest Dis*, **2020**, 90(2).

[4] Tang N, Li D, Wang X, et al., *J Thromb Haemost*, **2020**, 18(4):844-847.

[5] Kow CS, Sunter W, Bain A, et al.,*Am J Cardiovasc Drugs*, **2020**, 20(4):301-309.

[6] Zhou F, Yu T, Du R, et al., The Lancet, **2020**,395, 1054-62.

[7] Wang Y, Wang Y, Chen Y, et al., *J Med Virol*, **2020,**92(6): 568-576.

[8] Frater JL, Zini G, d'Onofrio G, et al., *Int J Lab Hematol*, **2020,**42(1):11-18.

[9] Levi M,Tachil J, Iba T, et al.,*Lancet Haematol*, **2020,**7(6):438-e440.

[10] Subramaniam S, Scharrer I., *Front Biosci (Landmark Ed)*, **2018**, 23: 1060-1081.

[11] Price LC, McCabe C, Garfield B, et al., *Eur Respir J*, **2020,** 56(1).

[12] Connors JM, Jerrold HL.,*Blood*, **2020,**135(23): 2033-2040.

[13] Fox SE, Akmatbekov A, Harbert JL, et al., *MedRxiv*, **2020**.

[14] N. Tang, D. Li, X Wang, et al.,*J Thromb Haemost*, **2020,**18(4): 844-847.