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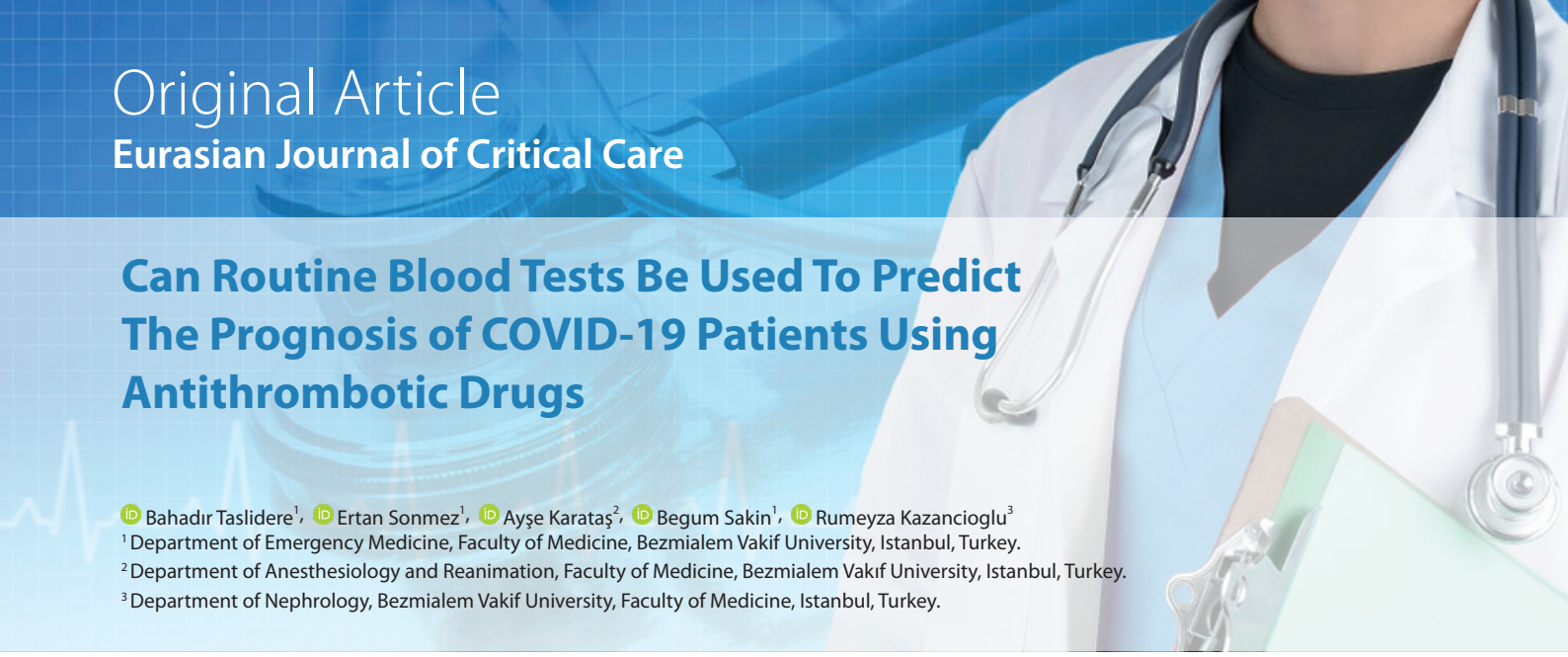

Can Routine Blood Tests Be Used To Predict The Prognosis of COVID-19 Patients Using Antithrombotic Drugs

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Abstract

Background: COVID-19 may predispose to thromboembolism due to excessive inflammation, hypoxia, and immobilization. We investigated whether these antithrombotic drugs are useful or harmful to tackle COVID-19 and which laboratory parameters are more usable for this purpose.

Materials and methods: In our study, patients diagnosed with COVID-19 while using antithrombotic drugs and COVID-19 patients who did not use antithrombotic drugs were compared. Demographic data, laboratory values, clinical results, duration of hospital stay, and mortality were noted and compared.

Results: The study was conducted on 236 patients admitted to the emergency department. The mean value of creatine, LDH, PT, NLR, troponin, and ferritin were higher in the drug-using group. Home quarantine and hospitalization rate was 68.8% (n = 33) in antiplatelet users, and 46.2% (n = 6) in the anticoagulant group.

Conclusion: The difference between the groups may have been caused by the number of chronic diseases and polypharmacy. The interaction of drugs used for the treatment of COVID-19 with antithrombotic agents is unknown. In addition, as the correlation between COVID-19 and thrombosis is not exactly known, adding antithrombotic drugs to the treatment of the disease is controversial. In our study, the biomarkers used to predict prognosis were worse in COVID-19 patients who continued antithrombotic therapy at the therapeutic dose. In the case of antithrombotic agents, the risks that may arise should always be considered. We recommend monitoring routine blood parameters, especially NLR, LDH, PT, APTT, troponin, and ferritin levels, for the prognosis monitoring of COVID-19 patients who will continue their current antithrombotic therapy

Keywords: COVID-19, antithrombotic, prognosis, biomarkers

Introduction

Thromboembolism is a serious, life-threatening clinical problem. Common risk factors include advanced age, immobility, inflammation, infections, and deep vein thrombosis. However, age-related comorbidities, complex polypharmacy, and drug–drug interactions cause increased risk. [1] Although venous stasis, endothelial damage, and hypercoagulation are among the mechanisms that play a role in the pathophysiology of the disease, there is another point to be considered. One rare virus that increases the predisposition to thrombosis is SARS-CoV 2. [2] Thromboembolic events are among the causes of increased morbidity and mortality in COVID-19. The incidence of thromboembolic complications in COVID-19 is between 8–27%. [3,4] The pulmonary thromboembolism rate detected in patients with COVID-19 in the intensive care unit is around 20%. [5] Therefore, The International Society on Thrombosis and Hemostasis (ISTH) recommends the use of antithrombotic drugs in COVID-19 patients. [6] There is currently no accepted approach to recommend the use of prophylactic anti-thrombolytics in COVID-19 patients, even if there are reasonable grounds for providing antithrombotic treatment. In addition, there is no evidence that it is beneficial for non-critical patients. [7,8] However, if anticoagulant therapy is required for patients diagnosed with COVID-19, coagulopathy symptoms should be followed closely. It is important to find suitable parameters for patient follow-up. In our study, COVID-19 patients who were already using antithrombotic agents due to chronic disease were compared with those who did not use the drugs. We investigated whether these antithrombotic drugs are useful or harmful in tackling COVID-19. For this purpose, we used routine blood test data—a potential diagnostic tool for COVID-19.

Materials and Methods

Our study, conducted between 03.11.2020 and 04.30.2020, included patients over the age of 18 who were admitted to the emergency department and diagnosed with COVID-19. Approval was obtained from the Ethics Committee of

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Bezmialem Vakıf University with the decision number 06/110, dated 05.05.2020. The data were retrospectively scanned with the International Classification of Diseases (ICD)- 10 code U07.3 (COVID-19) in the hospital registry. Patients with positive COVID-19 PCR tests or those who were compatible with COVID-19 pneumonia on thoracic tomography were included in the study. These patients were divided into two groups: those who used antithrombotic drugs and those who did not. The reported drugs used by patients were reached through the online prescription provision system. Demographic data, laboratory values, clinical results, and hospital stay duration were recorded. Those using antithrombotic drugs were divided into two groups (antiplatelet (AP) and anticoagulant (AC)) according to the pharmacological type of drugs. Blood samples obtained from the patients were analyzed, and complete blood count, lymphocyte count, neutrophil/lymphocyte ratio (NLR), C-reactive protein (CRP), kidney and liver parameters, cardiac enzymes, lactate dehydrogenase (LDH), coagulation parameters, D-dimer, ferritin, and electrolyte results were evaluated comparatively. Duration of hospital stay, clinical prognosis, and mortality of patients were noted. Ethics committee approval of the relevant institution and university was obtained for this retrospective study.

Consent to Participate: The informed consent process was waived (study conducted retrospectively, permission was obtained from the relevant institution)

Statistical analysis

The compliance of continuous variables to normal distribution was tested by Shapiro Wilk test. Descriptive statistics (mean, standard deviation (SD), minimum (Min.), median (Med.), maximum (Max.)) were used to define continuous variables. Comparison of more than two independent and non-normally distributed variables was made with the Kruskal Wallis test, while two independent, non-normally distributed variables were compared with the Mann-Whitney U test. Chi-Square (Fisher Exact test where appropriate) was used to examine the relationship between categorical variables. The statistical significance level was set at 0.05. The analyses were performed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013) Program.

Results

The study was conducted on 236 patients admitted to the emergency department, with a mean age of 57.56 ± 15.16 years (range: 19–93 years). There were 107 females (45.3%) and 129 males (54.7%) (Table 1). Eighty-two patients (34.7%) had no history of chronic disease, while 154 patients (65%) did. Among them, 84 patients (5.6%) had one chronic disease, and 70 patients (29.7%) had two or more. Sixty-one patients (25.8%) were using antithrombotic drugs, with 48 (78.6%) using antiplatelet agents; 13 (21.4%) were using anticoagulants, and 175 (74.2%) were not. Common chronic diseases among patients in the study; hypertension 68 patient (28.8%), diabetes mellitus 55 patient (23.3%), coronary artery disease 38 patient (16.1%), chronic lung diseases 34 patient (14.4 %), cerebrovascular diseases 11 patient (4.7 %), chronic kidney diseases 9 patient (3.8%), liver diseases 7 patient (3.0%) and malignancy 15 patient (6.4%) (Table 2). Among those using and not using antithrombotic medication, dyspnea (n=29, 47.5%) and dry cough (n=61, 34.9%) were the most common complaints, respectively, with significant differences between the groups (p=0.001). Desaturation was remarkable among the patients' vital signs using antithrombotic drugs (SO2: 89.97 ± 8.82) (p=0.012). NLR was significantly higher in patients using antithrombotic drugs (p <0.001). LDH was measured as 316 u/L in antithrombotic users and 291 u/L in non-users (p=0.002) (reference range (r.r.) 125–220). In patients using antithrombotic medication and non-users, PT was 18.19 ± 4.52 seconds and 14.8 ± 3.03 seconds, respectively, (r.r.=13.0–14.3) (p <0.001), PTT was 36.35 ± 15.25 sec and 31.86 ± 9.55, respectively, (r.r.=23–35) (p=0.028),

Table 1: Participant Demographics Table

		Mean (Std. dev.)	Range
Age in years		57,56±15,16	19-93
		Number	%
Gender	Female	107	45,3
	Male	129	54,7

Table 2: Drugs, Chronic Diseases and Outcome

		Number	%
Antithrombotic (AT) Drug	Non-users	175	74,2
	Users	61	25,8
Anticoagulant (AC) Drug	Non-users	223	94,5
	Users	13	5,5
Antiplatelet (AP) Drug	Non-users	188	79,7
	Users	48	20,3
Number of Comorbid Diseases	No history of chronic disease	82	34,7
	One chronic disease	84	35,6
	Two or more chronic diseases	70	29,7
Outcome	Discharged/ Home Quarantine	41	17,4
	Hospitalization (Services)	142	60,2
	Intensive Care Hospitalization	26	11,0
	Death	27	11,4

troponin was 72.5 pg/mL and 17.3 pg/mL (p <0.001), respectively, (r.r.=0–31), ferritin was 536 ng/mL and 352 ng/mL, respectively (r.r. 4.63–204) (p=0.043) (Table 3). There were no statistically significant differences in hospital stay duration regarding antithrombotic drug use (p=0.926). The rate of exitus and hospitalization were significantly higher in patients using antithrombotic drugs (p=0.002, p=0.011, respectively) (Table 4). We evaluated the results by grouping antithrombotic agents by type. The first group consisted of 48 people who used antiplatelet drugs (Acetylsalicylic acid 37.7%, Clopidogrel 36.1%, Ticagrelor 4.9%, Dipyridamole 1.6%). There were 13 people in the other group who were using anticoagulant drugs (Apixaban 6.6%, Dabigatran 4.9%, Rivaroxaban 4.9%, Warfarin 4.9%). Home quarantine and hospitalization rate was 68.8% (n = 33) in antiplatelet (AP) users, and 46.2% (n = 6) in the anticoagulant (AC) group. The intensive care and death rates were 31.3% (n = 15) in the AP group and 53.9% (n = 7) in the AC group (p = 0.040). According to the post-hoc pairwise comparison results, the systolic blood pressure, BUN, creatine, LDH, NLO, troponin average of AC users were high, and mean heart rate was low (p <0.05) (Table 5,6)

Table 3: Comparison of Laboratory Parameters According to Antithrombotic Drug Use

	Non-users	Users	P-value
	Mean (Std. dev.) Range	Mean (Std. dev.)W Range	
Body Temperature	37,09±1,08 37 (35-40)	36,88±1,08 36,7 (35-39)	0,236
Systolic Blood Pressure	129,47±25,54 127 (58-229)	140,48±29,95 136 (58-226)	0,004
Heart Rate	100,91±26,19 98 (40-260)	91,75±18,43 91 (43-136)	0,011
Pulse Oximetry (SpO2)	92,7±5,89 94 (62-100)	89,97±8,42 93 (60-99)	0,012
Blood Urea Nitrogen (BUN)	16,81±11,62 13 (5-92)	27,11±16,65 21 (7,48-69)	<0,001
Creatinine	1,03±0,86 0,81 (0,16-7)	1,48±1,54 0,95 (0,6-11)	0,001
Aspartate Transaminase	37,49±38,19 27 (9-445)	31,77±17,46 25 (9-74)	0,352
Alanine Transaminase	37,06±35,54 27 (7-326)	29,98±16,51 25 (9-82)	0,433
Potasyum	4,12±0,52 4 (2,46-6,89)	4,3±0,49 4,23 (3,5-5,5)	0,017
Lactate Dehydrogenase	291,51±223,35 246 (97-1825)	316,18±128,97 280 (56-686)	0,002
Prothrombin Time	14,82±3,03 15 (11-29)	18,19±4,52 17 (13,7-33)	<0,001
Partial Thromboplastin Time	31,86±9,55 33 (11-100)	36,35±15,25 34 (16-120)	0,028
International Normalized Ratio (INR)	1,27±0,2 1,23 (0,66-2,3)	1,36±0,39 1,24 (0,94-2,71)	0,907
White Blood Cell	6,96±3,24 6,1 (1,5-24)	8,4±4,06 7,98 (3,12-24)	0,011
Neutrophil-To-Lymphocyte Ratio (NLR)	3,47±2,06 2,7 (1,1-12)	6,04±5,34 4,4 (0,7-26)	<0,001
Platelet Count (PLT)	228,86±95,56 210 (66-651)	235,67±89,62 213 (102-482)	0,554
Platelet-To-Lymphocyte Ratio (PLR)	174,03±116,06 140 (20-806)	194,63±125,72 157 (50,1-586)	0,276
Mean Platelet Volume	7,71±1,59 7,5 (3,5-11,66)	7,8±1,51 7,68 (4,76-11,44)	0,631
Troponin	17,3±66,93 3,7 (0,2-746,8)	72,58±153,23 14 (1,1-800)	<0,001
D-dimer	468,94±727,09 246 (76-4111)	538,21±747,24 278 (138-3895)	0,056
Creatine Kinase	108,56±148,42 57 (0,1-1053)	83,74±98,01 56 (2-400)	0,464
C-reactive protein (CRP)	57,64±64,22 27,54 (0-295)	76,66±84,34 41 (0,44-304,2)	0,121
Ferritin	351,2±543,38 188 (19,5-4392)	536±834,4 256 (9,9-4800)	0,043

Mann-Whitney U test

Table 4: Outcomes According to Antithrombotic Drug Use

	Antithrombotic Drugs	Non-users		Users		p-value
		Number	%	Number	%	
Outcome	Discharged/ Home Quarantine	32	18,3	9	14,8	0,011
	Hospitalization (Services)	112	64,0	30	49,2	
	Intensive Care Hospitalization	18	10,3	8	13,1	
	Death	13	7,4	14	23,0	

Fisher's Exact test

Table 5: Comparison of Antiplatelet and Anticoagulant Drug Users

		Antiplatelet		Anticoagulant		p
		N	%	N	%	
Outcome	Discharged/ Home Quarantine	8	16,7	1	7,7	0,040
	Hospitalization (Services)	25	52,1	5	38,5	
	Intensive Care Hospitalization	3	6,3	5	38,5	
	Death	12	25,0	2	15,4	

Fisher's Exact test

Discussion

Patients with COVID-19 are at increased risk of thromboembolic events, especially concerning the critical situation and inactivity caused by this disease. Due to the difficulties in diagnosis, the reported incidence of these complications has a wide range of 8–20%. [3,9] Age, gender,

Table 6: Comparison of Laboratory Parameters According to Antiplatalet and Anticoagulant Usage

	Antiplatelet	Antıkoagülan	p-value
	Mean (Std. dev.) Range	Mean (Std. dev.) Range	
Body Temperature	36,93±1 36,75 (35-39)	36,72±1,34 36,1 (35-39)	0,412
Systolic Blood Pressure	144,69±27,91 140 (90-226)	124,92±33,18 130 (58-176)	0,103
Heart Rate	91,44±16,09 90,5 (63-136)	92,92±26,11 100 (43-136)	0,537
Pulse Oximetry (SpO2)	90,29±8,01 93 (60-99)	88,77±10,05 93 (60-96)	0,621
Blood Urea Nitrogen (BUN)	26,7±16,77 20,56 (7,48-69)	28,61±16,81 21,17 (10-68,22)	0,408
Creatinine	1,56±1,69 1,03 (0,6-11)	1,17±0,75 0,95 (0,66-3,45)	0,514
Lactate Dehydrogenase	314,81±133,3 276 (56-686)	321,23±116,35 297 (219-641)	0,731
Prothrombin Time	17,32±3,3 16,2 (13,7-27)	21,39±6,73 20 (13,7-33)	0,047

and the presence of chronic diseases stand out as risk factors. Comorbid diseases are more common in males than in females. [10] In our study, the patients' mean age was 57.56 ± 15.16 years, and 54.7% were male. About 25.8% (n=61) of 236 evaluated patients used antithrombotic agents due to their underlying medical conditions. Patients receiving antithrombotic therapy for underlying conditions are advised to continue these medications (at the same dose) if they are diagnosed with COVID-19. Similarly, all guidelines agree that other hospitalized patients with COVID-19 should receive prophylactic dose antithrombotic. Recent statements by the International Society on Thrombosis and Hemostasis (ISTH) recommend that all patients hospitalized with COVID-19 receive thromboprophylaxis or full-dose therapeutic anticoagulation. [11] A meta-analysis compared patients with COVID-19 treated with a prophylactic dose of anticoagulation with those treated with a therapeutic dose of anticoagulation. The results showed no difference between the two groups in terms of thromboembolism and mortality, [12,13] antithrombotic use at therapeutic doses is discussed in many similar studies. Until now, no joint decision has been identified that determines prophylactic and therapeutic antithrombotic use strategies. Studies showing the safety and efficacy of therapeutic anticoagulant doses in patients with COVID-19 are limited. Our research is valuable in this respect because we compared the prognosis of patients who used antithrombotic and those who did not, using routine blood tests for COVID-19 patients. Thus, we wanted to find out what laboratory values could guide patient management. Moreover, using routine blood tests is advantageous in terms of time and cost. COVID-19 patients are routinely tested for coagulopathy markers, such as D-dimer level, prothrombin time, neutrophil count, LDH, troponin, and platelet count. Laboratory parameters are used to monitor the course and prognosis of the disease. Predictors of disease outcomes in these patients need to be assessed to decrease morbidity and societal burden. For example, the American Society of Hematology should anticipate the need for intensive care; D-Dimer recommends monitoring PT, PTT, and platelet count. [14] Among the parameters examined in our study, the mean BUN, creatine, LDH, PT, PTT, WBC, NLR, Troponin, and Ferritin values were higher among the antithrombotic users. For example, studies have shown that the mortality rate increases when LDH is higher than 255 u/l. In our study, mean LDH was measured as 316 u/l. [15] Data in COVID-19 patients has suggested significant differences in LDH levels between antithrombotic users and non-drug users (p: 0,002). LDH is known to be found in lung tissue; severe infections can cause cytokine-mediated tissue damage and increase LDH release. Therefore, the severity of the disease in COVID-19 patients correlates with the increase in LDH. [16] COVID-19 patients using antithrombotic medication had significantly higher levels of PT, PTT than those without the thrombotic disease. There were no significant differences in levels of INR, D-DIMER, and PLT. PT and PTT are coagulating system factors that can be used for early diagnosis of DIC and had great value in disease prognosis. PT duration is an important finding in terms of coagulopathy, and in our study, it was longer than three seconds. In this case, it can be considered that patients transition from a high coagulation state to a fibrinolytic state due to excessive consumption of coagulation factors. [17] The neutrophil–lymphocyte ratio can help clinicians identify severe cases early, triage early, and initiate effective management. While NLR was 3.47 in those who do not use antithrombotic, it increased to 6.04 in those who did. [18] NLR has been shown to be an independent risk factor for severe disease. Another indicator of poor prognosis is troponin. Elevated troponin levels are common in patients with COVID-19 and are associated with fatal outcomes; [19] while it was 72.58 pg/ml in users, it was 17.3 pg/ml in the other group. The normal value of ferritin varies according to age and gender, so it should be in the range of 20–500 ml/ng. In our study, its mean value was 536 ng/ml among antithrombotic users. [20] The mortality rate was 11.4% (27 people) in the group using antithrombotic drugs and 7.4% in the other group. The patients in the antithrombotic drug user group had a higher case–fatality rate than the non-thrombotic disease group (p=0,011). This difference between mortalities may have been caused by the chronic diseases and polypharmacy because more than one drug is used to treat COVID-19 and the degree of interaction of these drugs with antithrombotic agents is unknown. However, it is known that antivirals used in treatment have such an interaction; [21,22] that is, drug–drug interactions can cause negative outcomes in patients. Hydroxychloroquine, azithromycin, oseltamivir, lopinavir, ritonavir, and favipiravir are frequently used

to treat COVID-19 patients in our country. As is known, lopinavir and ritonavir are potent cytochrome P450 3A4 inhibitors; therefore, they may increase the concentrations of direct-acting oral anticoagulants. [23] The rate of those with two or more chronic diseases was 65.3%. In our study, like various other studies, it was observed that the disease was more severe as the number of chronic diseases increased. [24] Even if the presence of chronic disease is important in the prognosis, it has been observed that it is more important to have two or more chronic diseases. Chronic diseases observed in our patients were hypertension (59%), diabetes mellitus (42.6%), heart diseases (32.8%), chronic lung diseases (24.6%), cerebrovascular diseases (13.1%), kidney diseases (11.5%), liver diseases (4.9%), and malignancy (4.9%). The incidence of diseases with high prevalence in the population was also high in our study. The high number of chronic diseases and drug–drug interactions due to the antivirals may worsen the prognosis. Since the mechanism between COVID-19 and thrombosis has not been fully explained, adding antithrombotic drugs to the treatment is controversial. In our study, the biomarkers used to predict prognosis were worse in COVID-19 patients who continued antithrombotic therapy at the therapeutic dose. We also evaluated the results by grouping antithrombotic agents by type. According to the results, the requirement for intensive care was higher in those using anticoagulant drugs. While the rate of intensive care admission and exitus was 31.3% in those using antiplatelet agents, this rate was 53.9% in those using anticoagulants. The mortality rate was higher in those using antithrombotic drugs compared to non-users. The mean value of BUN, creatine, LDH, PT, PTT, WBC, NLR, troponin, and ferritin were higher in the drug-using group. This difference between the groups may have been caused by the number of chronic diseases and polypharmacy.

Limitations

In the study, a single ICD code was scanned. Therefore, it is certain that it will miss COVID-19 cases that may be classified under different codes.

Conclusion

Antithrombotics should not be used in therapeutic doses for COVID-19. We recommend monitoring routine blood parameters, especially NLR, LDH, PT, PTT, troponin, and ferritin levels, for the prognosis monitoring of COVID-19 patients who will continue their current antithrombotic therapy.

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