Kocaeli Med J 2021;10;Özel sayı1;94-102

Nonvalvüler Atrial Fibrilasyon Nedeni ile Yeni Oral Antikoagülan veya Varfarin Kullanan Covid-19 Tanılı Hastaların D-dimer Düzeyleri ile Normal Sinüs Ritmindeki Covid-19 Tanılı Hastaların D-dimer Düzeylerinin Karşılaştırılması

Comparison between D-dimer Levels of Covid-19 Patients Using New Oral Anticoagulants or Warfarin Due to Nonvalvular Atrial Fibrillation and D-dimer Levels of Covid-19 Patients with Normal Sinus Rhythm

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ÖZ

GİRİŞ ve AMAÇ: *Koronavirüs hastalığı-19 (Covid-19), eşlik eden kalp hastalığı olan hastalarda kötü prognoza sahiptir ve yüksek mortalite ve tromboembolik olay oranlarına sahiptir.Bu çalışmanın amacı; Covid-19 lu nonvalvüler atrial fibrilasyon (AF) nedeni ile yeni oral antikoagülan veya varfarin kullanan hastaların D-dimer düzeyleri ile Covid-19'lu normal sinüs ritmindeki (NSR) hastaların D-dimer düzeylerinin karşılaştırılmasıdır.*

YÖNTEM ve GEREÇLER: *Bu çalışma retrospektif gözlemsel vaka-kontrol çalışmasıdır. Laboratuvar onaylı PCR pozitif Covid-19'lu hastalar ve PCR negatif fakat temas öyküsü, laboratuvar ve bilgisayarlı tomografi bulguları olan yüksek klinik şüphesi olan Covid-19'lu 50 (%0.11) si AF li ve 53 (%0.12) ü NSR olan toplam 103 ardışık hasta çalışmaya alındı. Benzer yaş ve cinsiyetteki uygun hastalar AF ve NSR grubu olarak ikiye bölündü. Hastaneye başvurudaki ve kontroldeki D-dimer düzeyleri karşılaştırıldı.*

BULGULAR: *Hastaneye kabulde, AF ve NSR grubundaki ortalama D-dimer seviyeleri sırasıyla 2.07 ± 4.41 µg/ml ve 1.89 ± 3.87 µg/ml idi: iki grup arasında istatistiksel olarak fark yoktu (p=0.345). Tedavinin beşinci gününde AF ve NSR grubundaki ortalama kontrol D-dimer seviyeleri sırasıyla 2.18 ± 3.31 µg/ml ve 2.06 ± 3.44 µg/ml idi: iki grup arasında istatistiksel olarak fark yoktu (p=0.814). İki grup arasında mortalite analizi yapıldığında hastaneye kabulde yaşayan Covid-19'lu hastaların ortalama D-dimer seviyeleri 1.40± 3.30 µg/ml iken yaşamayan Covid-19'lu hastaların D-dimer seviyeleri 4.41± 6.30 µg/ml idi: iki grup arasında belirgin fark vardı ve bu fark istatistiksel olarak anlamlı idi p= 0.020.*

TARTIŞMA ve SONUÇ: *Nonvalvüler AF nedeniyle NOAC veya varfarin kullanan hastalarda Covid-19 sürecinde tromboembolizm oranlarında ve D-dimer düzeylerinde artış izlenmedi. Literatürde, Covid-19 hastalarında AF'li ve NSR'de olanlar karşılaştırıldığında D-dimer düzeylerini ve tromboembolik oranlarını karşılaştıran çalışmaya rastlanmadı.*

Anahtar Kelimeler: *Covid-19, D-dimer, nonvalvüler atrial fibrilasyon, yeni oral antikoagülan, varfarin, tromboembolizm*

ABSTRACT

INTRODUCTION: *Coronavirus Disease 2019 (Covid-19) patients with concomitant cardiac diseases have poor prognosis and have high mortality and thromboembolic event rates. The aim of this study is to compare D-dimer levels of Covid-19 patients using new oral anticoagulants (NOAC) or warfarin due to nonvalvular atrial fibrillation (AF) and Covid-19 patients with normal sinus rhythm (NSR).*

METHODS: *It is an observational retrospective case-control study. 103 consecutive patients, 50 (0.11%) AF and 53 (0.12%) NSR with laboratory confirmed Covid-19 PCR positivity and patients who are PCR negative but have a high clinical suspicion of Covid-19 due to their contact history, laboratory and computed tomography findings were enrolled. The eligible patients of similar age and gender were divided into AF and NSR groups. Admission and control D-dimer levels were compared.*

RESULTS: *On admission mean D-dimer levels were 2.07 ± 4.41 µg/ml and 1.89 ± 3.87 µg/ml in the AF and NSR group, respectively: between two groups no statistically significant difference was found (p=0.345). Control D-dimer levels on the fifth day of treatment were 2.18 ± 3.31 µg/ml and 2.06 ± 3.44 µg/ml in the AF and NSR group, respectively: between two groups no statistically significant difference was found (p=0.814).*

DISCUSSION and CONCLUSION: *In patients using NOAC or warfarin due to nonvalvular AF, no increase in thromboembolism event rates and elevated D-dimer levels were observed during the Covid-19 process. There was no study in the literatüre that compared D-dimer levels and thromboembolic event rates of AF and NSR group with Covid-19 patients.*

Keywords: *Covid-19, D-dimer, nonvalvuler atrial fibrillation, new oral anticoagulant, warfarin, thromboembolism*

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Başvuru Tarihi: 26.10.2020
Kabul Tarihi: 15.01.2021

INTRODUCTION

Coronavirus Disease 2019 (Covid-19) was declared as a pandemic by the World Health Organization on March 11, 2020 and causes a serious increase in mortality and morbidity. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus responsible for the COVID-19 (1). In December 2019, an outbreak of a newtype of coronavirus was noted with a novel member of the coronavirus family. Bats are thought to be a viral reservoir, given the high homology of SARS-CoV-2 to other SARS-like viruses found in bats (2). Based on WHO data, there were 26 763 217 confirmed cases, 876 616 confirmed deaths in 216 countries, are as or territories worldwide at September 6 2020 (3). It is necessary to determine the critically ill patients applying to the hospital and to start treatment immediately. The intensity of anticoagulant therapy to be given alongside antiviral therapy should be adjusted according to the risk factors and laboratory findings.

D-dimer originates from the formation and lysis of cross-linked fibrin and reflects activation of coagulation and fibrinolysis (4). It has been reported that Covid-19 was associated with hemostatic abnormalities and markedly elevated D-dimer levels were observed (5). Severe Covid-19 can be complicated with coagulopathy, namely disseminated intravascular coagulation, which has a rather prothrombotic character with high risk of venous thromboembolism (VTE)(5-7). In a study of 449 patients with severe Covid-19 symptoms, anticoagulant therapy mainly with low molecular weight heparin (LMWH) appeared to be associated with lower mortality in the subpopulation meeting sepsis-induced coagulopathy criteria or with markedly elevated D-dimer (8).

Our hypothesis was that patients using warfarin or NOAC due to nonvalvular atrial fibrillation should not have increased risk of thromboembolism during the Covid-19 process. Besides, should additional anticoagulants be given? What is the effect of D-dimer levels at hospital admission on thromboembolism and mortality in these patients? The answers to these questions have not been evaluated yet.

METHODS

Study design

Study was an observational retrospective case-control study conducted in a pandemia hospital designated for Covid-19 patients. Of 4292 patients who were assessed and tested, first consecutive 50 (0.11%) confirmed Covid-19 positive AF patients enrolled then 53 (0.12%) confirmed Covid-19 positive NSR patients of similar age and gender were decected and enrolled into the study. A total of 103 adult (aged 18 years or older) patients admitted to our hospital between March 15, 2020 and July 15, 2020 were retrospectively screened. Patients younger than 18 years old were exculeded. The diagnosis of Covid-19 was established according to WHO interim guidance. (9) Patients with laboratory confirmed Covid-19 PCR positivity and patients who are PCR negative but have a high clinical suspicion of Covid-19 due to their contact history, clinical laboratory and computed thorax tomography findings were retrospectively enrolled in our study. Informed consent was obtained from all patients who participated in the study. The protocol was approved by the local ethics committee (approval date: 14.07.2020; approval number: 2020/87).

Data collection

All clinical, laboratory, and outcome data were extracted from electronic medical records using a standardized data collection form and patient's file from archive. All data were checked by two physicians.

Laboratory assay

Blood samples and PCR swabs were taken from patients who applied to the emergency service or pandemic outpatient clinics. Routine laboratory tests, blood count, coagulation profile, serum biochemical tests (including renal and liver function) high-sensitive cardiac troponin T, N-terminal pro-B-type natriuretic peptide were performed in the laboratory of the same hospital.

D-dimer was determined on Cobas T 511 automatic coagulation analyzer (Roche Diagnostics GmbH) by utilizing a latex-enhanced photometric immunoassay. Inter and intra-day variability coefficients were 3.41% and 4.22%.The laboratory reference range was 0-0.5 μg/ml. The D-dimer result was expressed in μg/ml FEU (Fibrinogen Equivalent Unit). All measurements were done within 2 hours

after blood sampling.

Electrocardiography was taken within 24 hours after admission. Transthoracic echocardiography reports were obtained from electronic medical records in the hospital data processing system.

Statistical analysis

Statistical analyses were performed with the IBM SPSS for Windows Version 21.0. Numerical variables were summarized as mean ± standard deviation. Categorical variables were given as frequencies and percentages. Categorical variables were compared by chi-square test. Normality of the continuous variables was evaluated by Kolmogorov–Smirnov test. Differences between the groups for continuous variables were determined by independent samples t test or Mann–Whitney U test as appropriate. Survival curves were presented by the Kaplan-Meier method and the curves between control and patient groups were compared by the log-rank test. A p value less than 0.05 was considered as significant.

RESULTS

Warfarin or NOAC treatments the patients used before Covid-19 were continued in the nonvalvular AF group if there was no contraindication. In patients using warfarin for AF, INR value was kept between 2-3. Standart thromboprophylaxis was given to the NSR group (enoxaparin 4000-10000 IU) based on D-dimer levels, body mass index, glomerular filtration rate and age (10).

Of 103 eligible patients; the median age was 72.57 years, ranging from 50 to 95 years, 81(78.6%) patients were older than 65 years and 53(51.5%) patients were female. The basic clinical characteristics of the patients, including age, gender, comorbidities are listed in Table 1. When two groups were compared, no difference was found in gender (p=0.62), age; <65 and>65; (p=0.12), diabetes mellitus (p=0.67), hyperlipidemia (p=0.69), coronary artery disease (p=0.11) and stroke history (p=0.34). In AF group, mean age was older (76.32, p<0.001) and hypertension (p<0.001), heart failure (p<0.001) and chronic obstructive pulmonary disease (p=0.04) was seen more frequently and there was a statistically significant difference.

The medications that patients use at admission are shown in Table 2. When the two groups were compared, the use of cardiac drugs were found to be higher in AF group. There was a statistically significant difference between the two groups (beta-blockers: n=29(58%) (p<0.001), diuretics: n=37(74%) (p<0.001), ACE inhibitors/angiotensin receptor blockers: n=27(54%) (p<0.001), spironolactone: n=6(12%) (p<0.011) and digoxin: n=7(14%) (p<0.005). On the other side, in NSR group the use of aspirin: n=13(24.5%) (p=0.020), clopidogrel: n=5(9.4%) (p<0.001) and oral antidiabetics: n=19(35.8%) (p=0.004) was higher and there was a statistically significant difference. When the two groups were compared, no difference was found in calcium channel blockers: (p=1.00), statins (p=1.00), insulin: (p=0.28) and doxazocin: (p=0.71).

Routine test results on admission are shown in Table 3. In AF group mean urea 65.02 ± 55.22 mg/dl (p=0.007) (normal range: 10-50mg/dl), mean creatinine 1.25 ± 0.68 mg/dl (p=0.04) (normal range: 0.5-0.95mg/dl), Rdw-SD 47.18 ± 6.31 fL (p<0.001) (normal range: 36.4-46.3 fL) and Rdw-CV 13.85±1.73% (p=0.001) (normal range: 11.7-14.4%) was higher and hemoglobin 11.66±1.93g/dl (p=0.031) (normal range: 11.7-16.0 g/dl) was lower and there was a statistically significant difference. High sensitive troponinT stat (TNT-HS) and proBNP were increased in both groups. TNT-HS was higher 41.59±110.51 ng/l (p=0.004)) (normal range: 0-14 ng/l) in NSR group and pro-BNP was higher 4201±6766.51 pg/mL (p=0.001) (normal range: 0-125 pg/ml) in AF group.

There was no statistically significant difference between the other parameters between the two groups (glucose, aspartate aminotransferase, alanine aminotransferase, sodium, potassium, lactate dehydrogenase, calcium, ferritin, C-reactive protein, white blood cell count, hematocrit, red blood cell count, mean corpuscular volume, neutrophil, eosinophil, basophil, lymphocyte, monocyte count, mean platelet volume, platelet large cell ratio).

Control D-dimer levels were measured at hospital admission and on the fifth day of treatment. Comparison of admission and control D-dimer levels between the two groups are shown in Table 4.

Mean D-dimer level in NSR group at admission was 1.89±3.87 μg/ml, mean D-dimer level of AF

patients was 2.07±4.41 µg/ml, mean D-dimer level of all patients was 1.97±4.09 µg/ml. Control mean D-dimer level in NSR group was 2.06±3.44 µg/ml, control mean D-dimer level in AF group was 2.18±3.31µg/ml and control mean D-dimer level of all patients was 2.12±3.36µg/ml. When the two groups were compared, there was no statistically significant difference between the D-dimer levels measured at both hospital admission and control.

When admission and control D-dimer levels were compared, there was no statistically significant difference between men and women in NSR and AF groups (p=0.707 and p=0.854; p=0.095 and p=0.897, respectively).

Patients who have underlying comorbidities (cardiovascular disease, diabetes mellitus, hypertension, cancer, chronic other immunosuppressive conditions, especially lung diseases), who are over 50 years old and have pneumonia symptoms such as fever, muscle / joint pain, cough and sore throat, whose SpO2 level is 90-93% in room air with a respiratory rate less than 30 per minute and have poor prognostic criterion in blood tests taken at admission (blood lymphocyte number less than 800/µl or CRP higher than 40 mg/l or ferritin higher than 500ng/ml or D-dimer which is higher than 1 µg/ml and have bilateral diffuse pneumonia findings on chest radiography or thorax computerized tomography were admitted to the pandemic ward.

Table 1. Baseline characteristics of 103 patients with COVID-19

Variable	NSR (n:53) n(%)	AF (n:50) n(%)	Total n(%)	p value
Age (year)	68.96 ± 9.40	76.32 ± 9.79	72.57 ±10.24	**<0.001**
Gender				
Female	29 (54.7)	24 (48.0)	53 (51.5)	0.628
Male	24 (71.7)	26 (52.0)	50 (48.5)	
Age				
< 65	15 (28.3)	7 (14.0)	22 (21.4)	0.126
≥ 65	38 (71.7)	43 (86.0)	81 (78.6)	
DM	19 (35.8)	15 (30.0)	34 (33.0)	0.674
HT	28 (52.8)	42 (84.0)	70 (68.0)	**0.001**
HL	7 (13.2)	9 (18.0)	16 (15.5)	0.690
CAD	8 (15.1)	15 (30.0)	23 (22.3)	0.114
HF	2(0,03)	25(50.0)	27 (26.2)	**<0.001**
COPD	15 (28.3)	25 (50.0)	40 (38.8)	**0.040**
Stroke history	6 (11.3)	10 (20.0)	16 (15.5)	0.346

AF: Atrial Fibrillation, DM: Diabetes mellitus, HT: Hypertension, HL: Hyperlipidemia, CAD: Coronary artery disease, HF: Heart Failure, COPD:Chronic Obstructive Pulmonary Disease , n: number

Table 2: Drugs used by patients on admission

Drugs	NSR (n:53) n(%)	AF (n:50) n(%)	Total n(%)	p value
warfarin	0	19 (38.0)	19 (18.4)	**<0.001**
rivaroxaban	0	14 (28.0)	14 (13.6)	**<0.001**
apixaban	0	12 (24.0)	12 (11.7)	**<0.001**
edoxaban	0	4 (8.0)	4 (3.9)	0.052
dabigatran	0	4(8.0)	4 (3.9)	0.052
bb	10 (18.9)	29 (58.0)	39 (37.9)	**<0.001**
ccb	20 (37.7)	18 (36.0)	38 (36.9)	1,000
diuretic	17 (32.1)	37 (74.0)	54 (52.4)	**<0.001**
acei-arb	18 (34.0)	27 (54.0)	45 (43.7)	**0,048**
clopidogrel	5 (9.4)	2 (4.0)	7 (6.8)	**<0.001**
aspirin	13 (24.5)	3 (6.0)	16 (15.5)	**0.020**
statin	6 (11.3)	5 (10.0)	11 (10.7)	1.000
oral ad	19 (35.8)	5 (10.0)	24 (23.3)	**0.004**

insulin	9 (17.0)	4 (8.0)	13 (12.6)	0.282
doxazosin	3 (5.7)	4 (8.0)	7 (6.8)	0.710
spironolactone	0 (%0)	6 (12.0)	6 (5.8)	**0.011**
digoxin	0 (%0)	7 (14.0)	7 (6.8)	**0.005**

bb: beta blokers, ccb: calcium channel blockers, acei: angiotensin-converting enzyme inhibitors, arb: angiotensin receptor blockers, oral ad: oral antidiabetic drugs

Table 3. Routine test results on admission

Variable	NSR (n:53) mean ± SD	AF (n:50) mean ± SD	Total(n=103) mean ± SD	p value
Urea mg/dL	45.85 ± 30.27	65.02 ± 55.22	55.25 ± 45.1	**0.007**
Cre mg/dL	1.07 ± 0.86	1.25 ± 0.68	1.16 ± 0.78	**0.040**
TNTHS ng/L	49.05 ± 160.11	35.41 ± 36.83	41.59 ± 110.51	**0.004**
BNP pg/L	285.84 ± 287.72	4201.29 ± 6766.51	2809.13 ± 5723.39	**<0.001**
Hb g/dL	12.47 ± 1.80	11.66 ± 1.93	12.08 ± 1.90	**0.031**
Rdw.sd fL	43.11 ± 5.39	47.18 ± 6.31	45.14 ± 6.19	**<0.001**
Rdw.cv %	13.85 ± 1.73	15.67 ± 3.37	14.76 ± 2.82	**0.001**

SD: Standard Deviation, TNTHS: Troponin T high sensitive stat, P.BNP: Pro-B type natriuretic peptide, Hb: Hemoglobin, Rdw-sd: Red blood cell distribution width-standart deviation, Rdw-cw: Red blood cell distribution width coefficient of variation

Table 4. Comparison of admission and control D-dimer levels between the two groups

Variable	NSR (n:53) mean ± SD	AF (n:50) mean ± SD	Total mean ± SD	p value
D-dimer 1	1.89 ± 3.87	2.07 ± 4.41	1.97 ± 4.09	0.345
D-dimer 2	2.06 ± 3.44	2.18 ± 3.31	2.12 ± 3.36	0.814
D-dimer 1				
<0.5	22 (41.5)	19 (46.3)	41 (43.6)	0.796
>0.5	21 (58.5)	22 (53.7)	53 (56.4)	
D-dimer 2				
<0.5	12 (31.6)	9 (28.1)	21 (30.0)	0.958
>0.5	26 (68.4)	23 (71.9)	49 (70.0)	

D-dimer 1: admission, D-dimer 2: control

Table 5. Hospital follow-up of Covid-19 patients

Variable	NSR (n:53) n(%)	AF (n:50) n(%)	Total n(%)	p value
Pandemic ward	38 (71.7)	34 (70.8)	72 (71.3)	1.000
ICU	14 (26.9)	13 (27.7)	27 (27.3)	1.000
MV	8(15)	10(20)	18(18.2)	1.000
non-survivors	10(19.2)	8(18.7)	18 (18.2)	1.000

ICU: Intensive care unit, MV: Mechanical ventilator

Table 6. Relationship between D-dimer levels studied at admission and control with mortality

Variable	Alive (n:82) mean ± SD or n(%)	Ex (n:18) mean ± SD or n(%)	Total mean ± SD or n(%)	p value
D-dimer 1	1.40 ± 3.30	4.41 ± 6.30	1.97 ± 4.09	**0,020**
D-dimer 2	1.51 ± 2.61	5.04 ± 4.92	2.12 ± 3.36	**<0.001**
D-dimer 1				
<0.5	37 (50.0)	4 (23.5)	41 (43.6)	0,088
>0.5	37 (50.0)	13(76.5)	53 (56.4)	
D-dimer 2				
<0.5	21 (36.2)	0 (0)	21 (30.0)	**0,013**
>0.5	37 (63.8)	12 (100.0)	49 (70.0)	
Follow-up time (day)	51.21 ± 35.03	13.39 ± 11.25	44.40 ± 35.20	**<0.001**

D-dimer 1: admission, D-dimer 2: control

Patients whose saturation fell below 90% despite the administration of O2 were taken to intensive care unit. Eight (15%) patients from the NSR group and ten (20%) patients from the AF group were connected to the mechanical ventilator. Ten patients from the NSR group (19.2%) and eight patients from the AF (16.7%) group died. When the two groups were compared, no statistically significant difference was found between the rates of admission to the pandemic ward and intensive care unit, requirement of mechanical ventilation and death rates. These findings are shown in Table 5. Comparison between the curves of those with and without AF according to their follow-up time is shown in Figure 1.

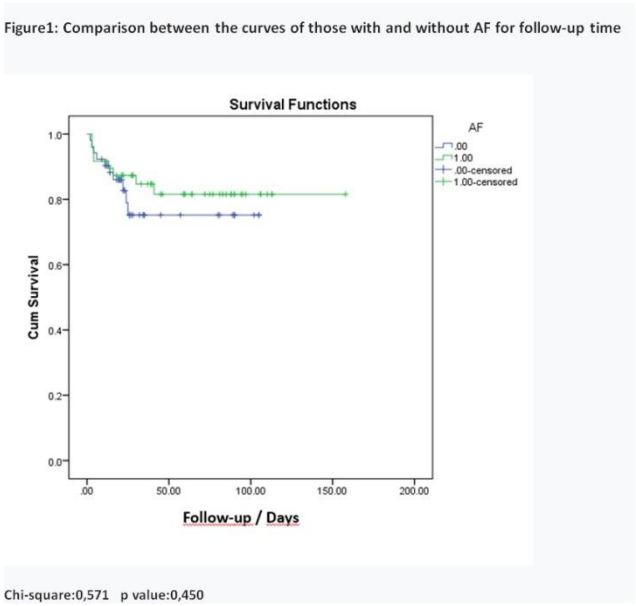

Figure 1. *Comparison between the curves of those with and without AF for follow-up time*

When mortality analysis was performed, the mean D-dimer level of living patients at admission to the hospital was 1.40±3.3; mean D-dimer level of non-survivors was 4.41±6.30 (p= 0.020).

Control mean D-dimer level of survivors was 1.51±2.61 µg/ml and control mean D-dimer level of non-survivors was 5.04±4.92 µg/ml (p<0.001). Control D-dimer level was not less than 0.5µg/ml in any of the patients who died. Patients who were discharged from hospitalization after the completion of their treatment were followed up for an average of 51.21 days and patients who died were followed for an average of 13.39 days. These findings are shown in Table 6. Comparison between the curves of those with and without AF for the time between admission and discharge dates is shown in Figure 2.

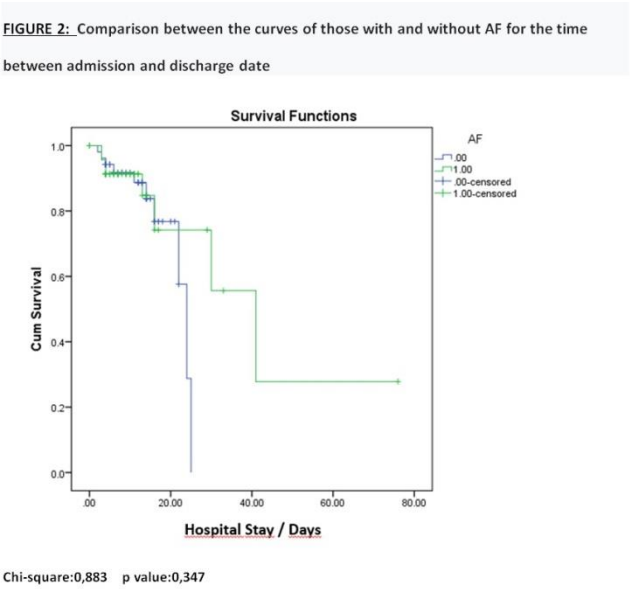

Figure 2. *Comparison between the curves of those with and without AF for the time between admission and discharge date*

DISCUSSION

After understanding the relationship of Covid-19 with coagulopathy, anticoagulants started to be used in treatment. The incidence of both arterial and venous thrombotic events was reduced after the use of anticoagulants.

Autopsy results guided us in understanding the relationship of Covid-19 with coagulopathy. The first autopsy series performed in USA. (11) All of the four patients tested in the autopsy series was positive for SARS-CoV-2 (by 2019 Novel Coronavirus Real Time RT-PCR). Notable laboratory findings were the development of elevated ferritin, fibrinogen, PT, and within 24 hours of death. When the specimens taken from autopsies were examined in the pathology laboratory, the following findings were found: the pulmonary arteries at the hilum were free of thromboembolism, there was diffusely edematous lung parenchyma, hemorrhage in the peripheral parenchyma, small and firm thrombi in sections of the peripheral parenchyma and absence of gross inflammation. Microscopic findings such as: mild to moderate lymphatic infiltrates (predominately in the interstitial space), CD4+ lymphocytes aggregated around small blood vessels that contained platelets and small thrombi, desquamated type-2 pneumocytes within the alveolar spaces, small vesicles believed to represent viral inclusions, thickening of alveolar capillaries with fibrin thrombi, entrapped neutrophils

and CD61+ megakaryocyte were obtained. Cardiomegaly and enlargement of the right ventricles were observed in the examined hearts. There was individual myocyte necrosis scattered with neighboring lymphocytes but coronary artery thrombosis was not seen in any of the four decedents on histologic examination. (12)

Magro et al. (13) reported on the autopsy findings from five decedents with severe Covid-19 infections and acute respiratory distress syndrome. They defined that tissue damage was complement-mediated. They described pauci-inflammatory capillary injury with mural and luminal fibrin deposition similar to the the other autopsy studies.

Platelets play an important role in the clearance of viral pathogens and platelet interactions with leukocytes trigger recruitment and tissue infiltration necessary for pathogen clearance. (14) Megakaryocytes actively produce platelets in the presence of Covid-19 infection. (12) The number of pulmonary megakaryocytes increases with infection, impaired lung function, cardiovascular disease and circulatory compromise. (15) An observation among patients with Covid-19, particularly those with severe illness, is an elevation of D-dimer in the peripheral blood. (16) D-dimer is formed as a result of the conversion of fibrinogen to fibrin using thrombin as a catalyst. (12)

The large case series of patients with Covid-19 (n = 5700) in the New York City area included baseline measurements of D-dimer. (16) In the previous studies, D-dimer elevation has been reported to be one of the most common laboratory findings noted in Covid-19 patients requiring hospitalization. Guanet al. analyzed 1099 patients with laboratory-confirmed Covid-19 from more than 550 hospitals in China (17) and found the nonsurvivors had a significantly higher D-dimer level (median, 2.12 μg/mL) than that of survivors (median, 0.61 μg/mL). Ning et al. also observed abnormal coagulation results, especially markedly elevated D-dimer in nonsurvivors with Covid-19. (18) Fei et al. conducted a retrospective study involved 191 patients with Covid-19 and found that D-dimer greater than 1 μg/mL on admission was associated with in-hospital mortality. (5) Huang et al. showed D-dimer levels on admission were higher in patients needing critical care support than those who did not require it (median, 0.5 μg/mL). (19) In their study, Litao Zhang et al. showed that hospital admission D-dimer level greater than 2 μg/mL was an independent predictor of in-hospital mortality indicator. (20) Until now, no study was conducted with the D-dimer levels of Covid-19 patients with AF. AF is an independent risk factor for stroke and is also associated with increased mortality above the age of 65 in both males and females. (21) This study compared the AF and NSR groups exposed to similar inflammatory and coagulopathy burden due to Covid-19. The expected high D-dimer levels, thromboembolism and mortality rate in AF group were not found. We think that it is low thanks to the warfarin and NOAC treatment they use and during Covid-19 treatment.

This study has several limitations. Firstly, our study might have selection bias because it was a single-center and retrospective study. Secondly, when compared to the general population, the number of patients using warfarin or NOAC due to nonvalvular AF is low and therefore, the number of patients that can be included in the study is low. Thirdly, PCR test for SARS-CoV-2 was not positive in all study patients. However, there were typical lesions suggestive of Covid-19 disease in computed tomography of all patients with the negative PCR test. In the previous studies, patients with positive tomography findings and negative first PCR test were shown to have positive results when repeated PCR tests were performed. (22-23)

CONCLUSION

In patients using NOAC or warfarin due to nonvalvular AF, no increase both thromboembolism event rates and elevated D-dimer levels were observed in these patients during the Covid-19 process in our study. We think that it is better to continue warfarin and NOAC treatment unless contraindicated. Studies with larger patient groups are required to develop oral or parenteral anticoagulant treatments that can be applied in Covid-19 treatment.

REFERENCES

1. Layton DS, Choudhary A, Bean AGD. Breaking the chain of zoonoses through biosecurity in livestock. Vaccine.

2017;35:5967-73.
2. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China Nature. 2020;579:265-9.
3. Corovavirus Disease (Covid-19), World Health Organization Situation Report on September 6, 2020. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200907-weekly-epi-update-4.pdf?sfvrsn=f5f607ee_2
4. Zhang L, Long Y, Xiao H, Yang J, Toulon P, Zhang Z. Use of D-dimer in oral anticoagulation therapy. International journal of laboratory hematology. 2018;40:503-7.
5. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis patients with novel coronavirus pneumonia. Journal of thrombosis and haemostasis. 2020;18:844-7.
6. Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? Eur Heart J. 2020;41:1858.
7. 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;18:1421-4.
8. Tang N, Bai H, Chen X, Gong J, LiD, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020. 2020;18:1094–9.
9. WHO Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance. 2020. Available from: https://www.who.int/publications/i/item/clinical-management-of-covid-19
10. Republic of Turkey Ministry of Health Covid-19 directory, science board study, 12 April 2020, Ankara. Available from: https://www.ekmud.org.tr/files/uploads/files/COVID-19_Rehberi-6.pdf
11. Fox SE, Akmatbekov A, Harbert JL, Li G, Brown JQ, VanderHeide RS. Pulmonary and Cardiac Pathology in Covid-19: The First Autopsy Series. April 10, 2020.medRxiv. Availablefrom: https://doi.org/10.1101/2020.04.06.20050 575
12. Richard C. Becker. COVID-19 update: Covid-19 associated coagulopathy. J Thromb Thrombolysis. 2020;50:54-67.
13. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Transl Res. 2020;220:1–13.
14. Guo L, Rondina MT. The era of thromboinflammation: platelets are dynamics sensors and effector cells during infectious diseases. Front Immunol 2019;10:2204
15. Sharma GK, Talbot IC. Pulmonary megakaryocytes: "missing link" between cardiovascular and respiratory disease? J ClinPathol.1986;39:969–76.
16. Becker RC. Covid-19 treatment update: follow the scientific evidence. J Thromb Thrombolysis. 2020;50:43-53.
17. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20.
18. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054-62.
19. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.
20. ZhangL, Yan X, Fan Q, Liu H, Liu X, Liu Z, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost. 2020;18:1324-9.
21. David Fitzmaurice. Atrial fibrillation and coagulation: who and when? Blood Reviews. 2009; 23:241-4.
22. Roncon L, Zuin M. Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome. J Clin Virol. 2020;127:104354.
23. Long C, Xu H, Shen Q, Zhang X, Fan B, Wang C, et al. Diagnosis of the Coronavirus disease (COVID-19): rRT-PCR or CT? Eur J Radiol. 2020;126:108961.