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Effect of Long-Term Use of Antithrombotics and Statins on COVID-19 Mortality and Clinical Severity

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ABSTRACT

Objective: Coronavirus Disease-2019 (COVID-19), has affected the whole world and is still an important disease with its mutations. In our study, we aimed to evaluate the effects of antithrombotic agents [acetylsalicylic acid (ASA), P2Y12 inhibitors, oral anticoagulants (OACs)] and statin treatments used before hospitalization on COVID-19 mortality and clinical severity.

Methods: A retrospective study was conducted on 5577 patients hospitalized with positive swab tests or findings consistent with COVID-19 on computed tomography. The 6-month mortality, in-hospital mortality, need for intensive care and intubation, and recurrent hospitalization outcomes of patients receiving chronic ASA (n=1210), P2Y12 inhibitors (n=357), OACs (n=1192), and statin (n=607) treatment were evaluated.

Results: The 6-month mortality rate was 13.5% (n=754), in-hospital mortality rate was 11.2% (n=627), the rate of admission to the intensive care unit was 16.1% (n=897), the need for intubation was 8.8% (n=493), and the rate of recurrent hospitalization was 10.4% (n=579). ASA and OACs reduced all outcomes. P2Y12 inhibitors provided benefit in other endpoints except intubation. Statins used before hospitalization did not provide a statistically significant decrease in 6-month mortality (p: 0.06), but were associated with a decrease in the rates of in-hospital mortality, need for intensive care, recurrent hospitalization, and intubation.

Conclusion: We found that long-term ASA, P2Y12 inhibitors, OACs and statin treatments used before hospitalization in patients hospitalized with COVID-19, reduced COVID-19 mortality and clinical severity. We think that these treatments may be beneficial in selected patient groups where post-COVID effects are observed.

Keywords: COVID-19, Antithrombotic, Statin, mortality

Introduction

Coronavirus Disease-2019 (COVID-19) is a viral disease caused by Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2). It was considered a pandemic between 2020 and 2022 and can still cause clinically significant diseases with mutations (Cucinotta & Vanelli, 2020). COVID-19 has affected more than 775 million people worldwide and caused more than 7 million deaths (World Health Organization. Number of COVID-19 cases reported to WHO, 2024). Its effects have been observed in many systems, mainly the pulmonary system, as well as the immunological, gastrointestinal, cardiac and neurological systems (Zaim et al., 2020).

An increased risk of cardiovascular (CV) complications such as myocarditis, cardiac arrhythmias, and arterial and venous thrombosis has been reported in COVID-19 patients (Madjid et al., 2020). Additionally, underlying cardiovascular disease (CVD) and/or CV risk factors such as dyslipidemia, smoking, obesity; increase the risk of serious clinical complications and death in COVID-19 patients (Task Force for the management of, 2022).

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It has been shown that fatal complications of SARS-CoV-2 infection are due to an overactive inflammatory response resulting in cytokine storms (Hojyo et al., 2020). Although pneumonia and acute respiratory distress syndrome (ARDS) are the main complications of COVID-19, serious thrombotic complications have been reported in patients and are associated with increased mortality (Malas et al., 2020). COVID-19 is a prothrombotic state characterized by inflammation and elevations of D-dimer, fibrin/fibrinogen degradation products, and these laboratory parameters have been suggested as markers of severe disease and worse prognosis (Tang et al., 2020).

SARS-CoV-2 causes typical lymphocytic endotheliitis leading to widespread endothelial inflammation and dysfunction (Varga et al., 2020). Endothelial dysfunction causes a shift of the homeostatic balance toward a procoagulant state, leading to platelet adhesion and aggregation, thus initiating a thromboinflammatory process (Yau et al., 2015). Subsequently, ARDS and hypercoagulation occur with the release of inflammatory cytokines, thrombin production and fibrin clot deposition (Abou-Ismail et al., 2020). Microvascular and macrovascular thrombosis have been observed in both venous and arterial systems with COVID-19 and are the cause of poor prognosis. In addition, high thromboembolic events have been reported despite the use of prophylactic anticoagulation in COVID-19 patients with comorbid diseases (Nopp et al., 2020).

Currently, there is no specific pharmacological recommendation for the treatment of COVID-19, but antiviral, immunomodulatory, anti-inflammatory and antithrombotic agents are used. In our study, we aimed to evaluate the effect of long-term use of antiplatelet agents [acetylsalicylic acid (ASA), P2Y12 inhibitors] oral anticoagulants (OACs) (warfarin, dabigatran, apixaban, edoxaban, rivaroxaban) and statins on COVID-19 mortality and clinical severity.

Methods

A total of 5577 patients who were admitted to the emergency department of Erzurum City Hospital between March and November 2020 and were diagnosed with COVID-19 by polymerase chain reaction (PCR) and/or computed tomography (CT), hospitalized, and started on treatment were included in our study. This study was conducted in accordance with the Declaration of Helsinki and with the approval of the local ethics committee. Ethics committee approval was received for this study from the ethics committee of Erzurum BEAH KAEK (Date: January 18, 2021, Number: 2021/02-33). Patient complaints, previous medical history, drug use history, clinical and demographic characteristics, hematological and biochemical parameters were identified from electronic medical records. Antiplatelet, anticoagulant, and statin treatments used by the patients in the last 1 year were recorded by identifying them in the National Medical Record System using the Social Security Institution website.

In accordance with the guidelines of the Ministry of Health of the Republic of Türkiye, COVID-19 diagnosis was made based on the patients' current complaints, contact history, physical examination findings, blood parameters, imaging findings, and PCR test results ("COVID-19 (SARS-CoV-2 ENFEKSİYONU) GENEL BİLGİLER, EPİDEMİYOLOJİ VE TANI ", 2020). Patients with a negative PCR test and no COVID-compatible findings on CT were not included in the study.

COVID-19 Definition

Possible cases admitted to Erzurum City Hospital between March 2020 and November 2022 were evaluated according to the guidelines of the Ministry of Health of the Republic of Türkiye. Oral and nasal swab samples were taken from patients with suspected COVID-19, and polymerase chain reaction (PCR) was used for molecular analysis. Pulmonary computerized tomography (CT) was applied to selected patients deemed appropriate by the examining clinician ("COVID-19 (SARS-CoV-2 ENFEKSİYONU) GENEL BİLGİLER, EPİDEMİYOLOJİ VE TANI ", 2020). Complete blood count (CBC), inflammation parameters (C-reactive protein, ferritin) and biochemistry tests are routinely performed on patients all suspected patients with COVID-19. A second swab sample was taken from hospitalized patients when the first sample was negative. When one of the two samples taken was positive, the patient was diagnosed with COVID-19, and if both were negative, and the CT was negative, COVID-19 was excluded.

ICU Admission Criteria

In the cases specified in the guideline, the patients were evaluated by the relevant clinician, and the need for intensive care was decided ("COVID-19 (SARS-CoV-2 ENFEKSİYONU) ERİŞKİN HASTA TEDAVİSİ," 2020).

- Patient with dyspnea and respiratory distress despite of oxygen therapy and in the follow-up, the oxygen requirement increased.
- Respiration rate ≥ 30/min
- $PaO_2/FiO_2 < 300$

Table 1: Baseline characteristics of patients

Characteristics	All Patients (n= 5577)	Survivors (n=4823)	Nonsurvivors (n=754)	P Value
Age (year)	61.4±16.4	59.5±16.2	74.1±11.3	**<.001**
Gender (Male, %)	2777 (49.8)	2317 (48)	460 (61)	**<.001**
HT (number, %)	2760 (49.5)	2274 (47.1)	486 (64.5)	**<.001**
DM (number, %)	1505 (27)	1282 (26.6)	223 (29.6)	.086
CAD (number, %)	1188 (21.3)	963 (20)	225 (29.8)	**<.001**
HF (number, %)	294 (5.3)	211 (4.4)	83 (11)	**<.001**
COPD (number, %)	765 (13.7)	585 (12.1)	180 (23.9)	**<.001**
CVD (number, %)	125 (2.2)	100 (2.1)	25 (3.3)	**.032**
AF (number, %)	368 (6.6)	247 (5.2)	121 (16.1)	**<.001**
HL (number, %)	686 (12.3)	599 (12.4)	87 (11.5)	.501
CRF (number, %)	146 (2.6)	104 (2.2)	42 (5.6)	**<.001**
Asthma (number, %)	228 (4.1)	207 (4.3)	21 (2.8)	.052
Medications				
ASA (number, %)	1210 (21.7)	1013 (21)	197 (26.1)	**.001**
P2Y12 inhibitors (number, %	357 (6.4)	295 (6.1)	62 (8.2)	**.028**
Anticoagulants (number, %)	1192 (21.4)	1092 (22.6)	100 (13.3)	**<.001**
Statins (number, %)	607 (10.9)	510 (10.6)	97 (12.9)	.060
ACEI / ARB (number, %)	1908 (34.2)	1601 (33.2)	307 (40.7)	**<.001**
BB (number, %)	1159 (20.8)	972 (20.2)	187 (24.8)	**.003**
CCB (number, %)	972 (17.4)	792 (16.4)	180 (23.9)	**<.001**
Diuretics (number, %)	1682 (30.2)	1399 (29)	283 (37.5)	**<.001**
Laboratory				
Hb (g/dL)	13.3 (12.1-14.4)	13.4 (12.3-14.4)	12.3 (10.4-14.3)	**<.001**
Htc (%)	41.1 (37.8-44.2)	41.2 (38.2-44.1)	39 (33.3-44.9)	**<.001**
Wbc (10^3/µL)	7.21 (5.53-9.55)	6.93 (5.36-8.93)	10.45 (7.61-13.87)	**<.001**
Neutrophil count (10^3/µL)	5.18 (3.58-7.49)	4.82 (3.43-6.82)	8.95 (6.13-11.89)	**<.001**
Lymphocyte count (10^3/µL)	1.23 (0.86-1.68)	1.30 (0.95-1.73)	0.71 (0.49-1.03)	**<.001**
Platelet count (10^3/µL)	231.7 (184-289.2)	238 (190.8-295)	190.6 (144.4-242.4)	**<.001**
AST (U/L)	33 (24.5-47.5)	31.3 (23.7-43.5)	53.4 (34.8-101)	**<.001**
ALT (U/L)	31.3 (21-49.5)	31 (21-47.5)	35.3 (21.8-70.7)	**<.001**
Ferritin, (ng/mL)	257.4 (111.4-547.7)	229.1 (98.1-467.1)	595.9 (280.5-1119.5)	**<.001**
LDH (U/L)	297.6 (236-384)	283.1 (229.5-353.5)	482 (368.4-625.8)	**<.001**
CRP (mg/L)	36.8 (12.8-75.7)	30.8 (10.3-62.5)	95.6 (53.1-145.9)	**<.001**
D-dimer (µg/mL)	384 (104-1318)	302 (91-956)	2540 (768.5-7500)	**<.001**
Procalcitonin (ng/mL)	0.11 (0.02-0.57)	0.08 (0.01-0.35)	1.07 (0.335-3.32)	**<.001**
pH level	7.40 (7.38-7.44)	7.40 (7.37-7.43)	7.44 (7.40-7.45)	**.046**
Lactic acid (mmole/L)	2.1 (1.6-2.7)	2 (1.6-2.6)	2.75 (2.1-3.6)	**<.001**
Troponin I (ng/mL)	0.011 (0.003-0.1)	0.008 (0.002-0.033)	0.265 (0.057-1.375)	**<.001**
NTproBNP (pg/mL)	444 (83.8-4916.5)	159 (46.2-702.5)	7074 (1704-20911.7)	**<.001**
Creatinine (mg/dL)	0.88 (0.73-1.12)	0.85 (0.72-1.06)	1.28 (0.94-1.95)	**<.001**
Na (mmol/L)	137 (134.6-139.1)	136.7 (134.5-138.9)	139.5 (135.8-143.9)	**<.001**
K (mmol/L)	4.18 (3.89-4.49)	4.15 (3.88-4.44)	4.40 (4.03-4.85)	**<.001**
Glucose (mg/dL)	131 (136-179.3)	126.7 (104-172)	162.2 (129.1-208)	**<.001**
Albumin (g/L)	3.8 (3.4-4.1)	3.8 (3.5-4.1)	3.15 (2.86-3.52)	**<.001**
INR	1.07 (1-1.18)	1.07 (1-1.18)	1.08 (1-1.20)	.153
TG (mg/dL)	128 (94.3-179)	126.5 (93.3-126.8)	138.3 (104.2-192.5)	**<.001**
HDL (mg/dL)	33.5 (27.2-41.2)	34.1 (28-41.7)	28.6 (22.4-36.6)	**<.001**
LDL (mg/dL)	86 (67-109)	88 (69.4-110.8)	72.5 (54.3-96.5)	**<.001**
COVID-19 PCR test (positive, %)	3809 (68.3)	3300 (68.4)	509 (67.5)	.615
Lung involvement in tomography (positive, %)	4753 (85.2)	4075 (84.5)	678 (89.9)	**<.001**

Abbreviations: HT: hypertension, DM: diabetes mellitus, CAD: coronary artery disease, HF: heart failure COPD: chronic obstructive pulmonary disease, CVD: cerebrovascular disease, AF: atrial fibrillation HL: hyperlipidemia, CRF: chonic renal failure, ASA: acetylsalicylic acid ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin reseptor blocker, BB: beta blocker, CCB: calcium channel blockers, Hb: haemoglobin, Htc: hematocrit, Wbc: white blood cell, AST: aspartate aminotransferase, ALT: alanine aminotrasferase, LDH: Lactate dehydrogenase, CRP: C-reactive protein, NTproBNP: N-terminal probrain natriuretic peptide, Na: sodium, K: potassium, INR: International Normalized Ratio, TG: triglycerides, HDL: high density lipoprotein, LDL: low density lipoprotein, PCR: polymerase chain reaction

- SpO2 < 90% or PaO2 < 70 mmHg despite 5 L/min oxygen therapy
- Hypotension (systolic blood pressure < 90 mmHg and more than 40 mmHg decrease from normal systolic blood pressure and mean arterial pressure < 65 mmHg, tachycardia > 100/min
- Patients with acute kidney injury, acute liver function tests, confusion, acute organ dysfunction such as acute bleeding diathesis and immunosuppression
- Troponin elevation and arrhythmia
- Lactate > 2 mmol
- Presence of skin disorders such as capillary return disorder and cutis marmaratus

The study endpoints were determined as 6-month mortality, in-hospital mortality, need for intensive care, need for intubation, and re-hospitalization, and the results were retrospectively obtained from electronic medical records.

Statistical analysis

Data were analyzed using the SPSS 23.0 version (IBM, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (interquartile range), and categorical variables were expressed as percentages. Whether continuous variables fit the normal distribution was determined using the "Homogeneity of Variance" test. Continuous variables were compared using "Student's t-test" and "Mann–Whitney U test" as appropriate. Categorical variables were compared using the "chi-square" test. Variables were considered statistically significant when the *p* value was <.05.

Results

The mean age of 5577 patients included in our study was 61.4 ± 16.4 years and 49.8% were male. PCR test was positive in 3809 (68.3%) patients and COVID-19 findings were observed in computed tomography of 4753 (85.2%) patients. The most common comorbidity in patients was hypertension (n=2760 (49.5%). Mortality was observed in 754 patients; these patients were older (74.1 ± 11.3) and 61% were male. Among those with mortality, the most common comorbidity was hypertension with 64.5%. D-Dimer, troponin, crp, ferritin, NTproBNP were higher in patients with mortality. Baseline demographic data of the study population are shown in Table-1.

Before admission, 21.8% of the patients were using ASA, 24.4% were using OACs, 6.4% were using P2Y12 inhibitors and 1.9% were using statins (Figure-1). In addition, the rates of other medications used by the patients before admission are shown in Table-1.

When the study endpoints were examined, the 6-month mortality rate was 13.5%, the in-hospital mortality rate was 11.2%, the rate of patients need intensive care was 16.1%, the rate of patients intubated was 8.8%, and the rate of recurrent hospitalization was 10.4% (Table 2).

According to the study results, ASA and OACs used before hospitalization reduced the 6-month mortality, in-hospital mortality, need for intensive care, recurrent hospitalizations and need for intubation outcomes. P2Y12 inhibitors provided benefit in other endpoints except intubation. Statins used before hospitalization did not provide a significant reduction in 6-month mortality (p: 0.06) but were associated with a reduction in in-hospital mortality, need for intensive care, recurrent hospitalizations and intubation rates (Table 3).

Table 2: Course of the COVID-19 disease

	All Patients (n = 5577)
Total mortality (number, %)	754 (13.5)
In-hospital mortality (number, %)	627 (11.2)
Need for intensive care (number, %)	897 (16.1)
Need for intubation (number, %)	493 (8.8)
Recurrent hospitalization (number, %)	579 (10.4)

Discussion

Acetylsalicylic acid (ASA)

Acetylsalicylic acid (ASA) inhibits platelet functions by irreversibly inhibiting cyclooxygenase (COX) activity. Low doses show an antithrombotic effect by inhibiting the formation of thromboxane A2 by acetylation of COX-1, while higher doses block prostaglandin production by inhibiting COX-1 and COX-2, resulting in analgesic, anti-inflammatory and antipyretic effects (Pillinger et al., 1998). ASA also has antiviral and immunomodulatory effects. Studies have shown that ASA reduces the production of interleukin-6 (IL-6), C-reactive protein (CRP) and macrophage colony stimulating factor (Glatthaar-Saalmuller et al., 2017; Ikonomidis et al., 1999). Additionally, ASA has been associated with prevention of ARDS and protection from acute lung injury and reduced mortality (Boyle et al., 2015; Panka et al., 2017). Researchers have suggested ASA and other antiplatelet therapies as potential agents in COVID-19 due to the high burden of microvascular thrombosis (Bikdeli et al., 2020). Similarly, we think that the beneficial effects of aspirin in our study are due to its anti-inflammatory, analgesic,

antithrombotic, antipyretic, antiviral and immunomodulatory effects.

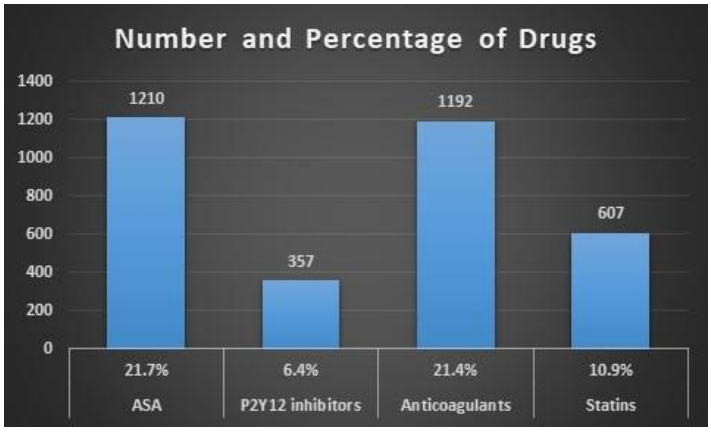

Figure 1: Drug use in COVID-19 patients

P2Y12 Inhibitors

Researchers have suggested antiplatelet treatments in COVID-19 patients due to the high burden of thrombosis (Bikdeli et al., 2020). Additionally, antiplatelet therapy has been shown to have beneficial effects on ARDS, acute lung injury, sepsis and mortality (Du et al., 2018; Wang et al., 2016). However, there are many unknowns regarding the use and benefits of P2Y12 inhibitors in COVID-19. It is not known which stage of the disease will respond best, nor is it known what agent and dose are most appropriate to provide maximum effect while reducing bleeding risks. In addition, thrombocytopenia is associated with an increased risk for worse clinical outcomes with COVID-19 (Lippi et al., 2020). It has been recommended that antiplatelet therapy be used with caution in the presence of clinical conditions such as concomitant coronary artery disease and acute coronary syndrome in COVID-19 patients (Bikdeli et al., 2020). Similarly, in our study, we observed less mortality and better clinical status in patients using P2Y12 inhibitors.

Anticoagulants

Thromboprophylaxis with anticoagulants, particularly low molecular weight heparin (LMWH), has been shown to be beneficial in reducing the risk of COVID-19 complications and mortality and is recommended for all hospitalized patients with COVID-19 ("COVID-19 (SARS-CoV-2 ENFEKSİYONU) ERİŞKİN HASTA TEDAVİSİ," 2020; Moores et al., 2020). The use of vitamin K antagonists and direct oral anticoagulants (DOACs) in the treatment of COVID-19 is controversial, and switching from oral anticoagulation to LMWH is recommended in patients hospitalized with COVID-19 infection (Moores et al., 2020; Testa et al., 2020). Various studies have been conducted on the effects of anticoagulant treatments used before hospitalization on COVID-19 outcomes, and conflicting results have been observed. While there are studies that show no difference in clinical outcomes between patients treated with VKAs and DOACs (Spiegelenberg et al., 2021), there are also studies that independently associate long-term oral anticoagulation with DOACs or VKAs with better outcomes (Frohlich et al., 2021). In our study, although it is not clearly known whether these drugs were continued during the hospitalization of patients using chronic OACs and it is thought that they were probably switched to LMWH, we observed that there was a relationship between mortality and the severity of COVID-19 in patients using chronic OACs.

Statins

Statins are lipid-lowering drugs and used to prevent CV events (Grundy et al., 2019). The effects of statins on COVID-19 are unclear. Some studies report no difference in mortality and severe infection outcomes, while others even show adverse outcomes in statin users compared with non-users (Butt et al., 2020; Hariyanto & Kurniawan, 2020, 2021). However, many studies have found that statin use is associated with a reduced risk of mortality, reduced risk of adverse outcomes, reduced disease severity, and reduced recovery time in COVID-19 patients (Cariou et al., 2021; Kow & Hasan, 2020; Pal et al., 2022). Overall, there were more arguments in favor of continuing use rather than interrupting statin therapy in patients with COVID-19. In our study, although the total mortality was low in number, no statistically significant difference was observed. This

Table 3: Effects of antithrombotic drugs and statins on the course of the disease

	6-months Mortality	In-hospital Mortality	Need for Intensive Care	Need for Intubation	Recurrent Hospitalization
ASA	**0.001**	**0.001**	**<0.001**	**0.021**	**<0.001**
P2Y12 inhibitors	**0.028**	**0.026**	**<0.001**	0.152	**<0.001**
OACs	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Statins	0.060	**0.023**	**<0.001**	**0.013**	**<0.001**

Abbreviations: ASA: acetylsalicylic acid, OACs: oral anticoagulants

situation can be explained by the relatively low number of statin use. Additionally, in our study, a decrease in in-hospital mortality and COVID-19 severity was observed in patients using statins.

Post-COVID Syndrome

Post-COVID syndrome has been defined as signs and symptoms that develop during or after COVID-19 infection, are present for more than 12 weeks, and cannot be attributed to alternative diagnoses (Shah et al., 2021). The most common symptoms are fatigue and breathlessness. Symptoms may be singular, multiple, constant, transient, or fluctuating, and canchange in natüre over time. Potential mechanisms contributing to the pathophysiology of post-COVID may be driven by tissue damage caused by virus-specific changes or long-lasting inflammatory response, immune dysregulation, and autoimmune reactions. Currently, management options are limited because there is insufficient data of post-COVID. It must be a personalized approach involving monitoring ongoing symptoms and late complications, symptomatic treatment, palliative care, physical rehabilitation, mental health, and psycho-social support. In a personalized approach in post-COVID patients, the use of antithrombotics and statins can be considered, especially in cases of cardiac complications.

Limitations

Our study has some limitations common to retrospective studies. Data on the duration and dosage of medications used before admission and whether they were continued during hospitalization are limited. We have limited data regarding the anticoagulation dose that patients receive while in the intensive care unit. We also did not evaluate the interaction of these drugs with other potential treatments for COVID-19, such as antiviral drugs, or the impact of in-hospital interventions that may affect outcomes. Our study evaluated hospitalized patients and cannot be generalized to asymptomatic or symptomatic non-hospitalized patients. Also, since it is a single center study, its generalization to the entire population is limited.

Conclusions

We observed that long-term ASA, P2Y12 inhibitors, OACs and statin treatments used before hospitalization in patients hospitalized with COVID-19, reduced COVID-19 mortality and clinical severity. We think that these drugs can be given to selected individuals in patient groups defined as post-COVID and with ongoing active complaints.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Erzurum BEAH KAEK (Date: January 18, 2021, Number: 2021/02-33).
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References

Abou-Ismail, M. Y., Diamond, A., Kapoor, S., Arafah, Y., & Nayak, L. (2020). The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. *Thrombosis Research, 194*, 101-115. https://doi.org/10.1016/j.thromres.2020.06.029

Bikdeli, B., Madhavan, M. V., Jimenez, D., Chuich, T., Dreyfus, I., Driggin, E., … Right Ventricular, F. (2020). COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. *Journal of the American College of Cardiology, 75*(23), 2950-2973. https://doi.org/10.1016/j.jacc.2020.04.031

Boyle, A. J., Di Gangi, S., Hamid, U. I., Mottram, L. J., McNamee, L., White, G., … McAuley, D. F. (2015). Aspirin therapy in patients with acute respiratory distress syndrome (ARDS) is associated with reduced intensive care unit mortality: a prospective analysis. *Critical Care, 19*(1), 109. https://doi.org/10.1186/s13054-015-0846-4

Butt, J. H., Gerds, T. A., Schou, M., Kragholm, K., Phelps, M., Havers-Borgersen, E., … Fosbol, E. L. (2020). Association between statin use and outcomes in patients with coronavirus disease 2019 (COVID-19): a nationwide cohort study. *BMJ Open, 10*(12), e044421. https://doi.org/10.1136/bmjopen-2020-044421

Cariou, B., Goronflot, T., Rimbert, A., Boullu, S., Le May, C., Moulin, P., … investigators, C. (2021). Routine use of statins and increased COVID-19 related mortality in inpatients with type 2 diabetes: Results from the CORONADO study. *Diabetes & Metabolism, 47*(2), 101202. https://doi.org/10.1016/j.diabet.2020.10.001

Cucinotta, D., & Vanelli, M. (2020). WHO Declares COVID-19 a Pandemic. *Acta Biomedica, 91*(1), 157-160. https://doi.org/10.23750/abm.v91i1.9397

Du, F., Jiang, P., He, S., Song, D., & Xu, F. (2018). Antiplatelet Therapy for Critically Ill Patients: A Pairwise and Bayesian Network Meta-Analysis. *Shock, 49*(6), 616-624. https://doi.org/10.1097/SHK.0000000000001057

Frohlich, G. M., Jeschke, E., Eichler, U., Thiele, H., Alhariri, L., Reinthaler, M., … Gunster, C. (2021). Impact of oral anticoagulation on clinical outcomes of COVID-19: a nationwide cohort study of hospitalized patients in Germany. *Clinical Research in Cardiology, 110*(7), 1041-1050.

https://doi.org/10.1007/s00392-020-01783-x

Glatthaar-Saalmuller, B., Mair, K. H., & Saalmuller, A. (2017). Antiviral activity of aspirin against RNA viruses of the respiratory tract-an in vitro study. *Influenza and Other Respiratory Viruses, 11*(1), 85-92. https://doi.org/10.1111/irv.12421

Grundy, S. M., Stone, N. J., Bailey, A. L., Beam, C., Birtcher, K. K., Blumenthal, R. S., … Yeboah, J. (2019). 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology, 73*(24), 3168-3209. https://doi.org/10.1016/j.jacc.2018.11.002

Hariyanto, T. I., & Kurniawan, A. (2020). Statin therapy did not improve the in-hospital outcome of coronavirus disease 2019 (COVID-19) infection. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 14*(6), 1613-1615. https://doi.org/10.1016/j.dsx.2020.08.023

Hariyanto, T. I., & Kurniawan, A. (2021). Statin and outcomes of coronavirus disease 2019 (COVID-19): A systematic review, meta-analysis, and meta-regression. *Nutrition, Metabolism & Cardiovascular Diseases, 31*(6), 1662-1670. https://doi.org/10.1016/j.numecd.2021.02.020

Hojyo, S., Uchida, M., Tanaka, K., Hasebe, R., Tanaka, Y., Murakami, M., & Hirano, T. (2020). How COVID-19 induces cytokine storm with high mortality. *Inflammation and Regeneration, 40*, 37. https://doi.org/10.1186/s41232-020-00146-3

Ikonomidis, I., Andreotti, F., Economou, E., Stefanadis, C., Toutouzas, P., & Nihoyannopoulos, P. (1999). Increased proinflammatory cytokines in patients with chronic stable angina and their reduction by aspirin. *Circulation, 100*(8), 793-798. https://doi.org/10.1161/01.cir.100.8.793

Kow, C. S., & Hasan, S. S. (2020). Meta-analysis of Effect of Statins in Patients with COVID-19. *American Journal of Cardiology, 134*, 153-155. https://doi.org/10.1016/j.amjcard.2020.08.004

Lippi, G., Plebani, M., & Henry, B. M. (2020). Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. *Clinical Chimica Acta, 506*, 145-148. https://doi.org/10.1016/j.cca.2020.03.022

Madjid, M., Safavi-Naeini, P., Solomon, S. D., & Vardeny, O. (2020). Potential Effects of Coronaviruses on the Cardiovascular System: A Review. *JAMA Cardiology, 5*(7), 831-840. https://doi.org/10.1001/jamacardio.2020.1286

Malas, M. B., Naazie, I. N., Elsayed, N., Mathlouthi, A., Marmor, R., & Clary, B. (2020). Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. *EClinicalMedicine, 29*, 100639. https://doi.org/10.1016/j.eclinm.2020.100639

Moores, L. K., Tritschler, T., Brosnahan, S., Carrier, M., Collen, J. F., Doerschug, K., … Wells, P. (2020). Prevention, Diagnosis, and Treatment of VTE in Patients With Coronavirus Disease 2019: CHEST Guideline and Expert Panel Report. *Chest, 158*(3), 1143-1163. https://doi.org/10.1016/j.chest.2020.05.559

Nopp, S., Moik, F., Jilma, B., Pabinger, I., & Ay, C. (2020). Risk of venous thromboembolism in patients with COVID-19: A systematic review and meta-analysis. *Research and Practice in Thrombosis and Haemostasis, 4*(7), 1178-1191. https://doi.org/10.1002/rth2.12439

Pal, R., Banerjee, M., Yadav, U., & Bhattacharjee, S. (2022). Statin use and clinical outcomes in patients with COVID-19: An updated systematic review and meta-analysis. *Postgraduate Medical Journal, 98*(1159), 354-359. https://doi.org/10.1136/postgradmedj-2020-139172

Panka, B. A., de Grooth, H. J., Spoelstra-de Man, A. M., Looney, M. R., & Tuinman, P. R. (2017). Prevention or Treatment of ARDS With Aspirin: A Review of Preclinical Models and Meta-Analysis of Clinical Studies. *Shock, 47*(1), 13-21. https://doi.org/10.1097/SHK.0000000000000745

Pillinger, M. H., Capodici, C., Rosenthal, P., Kheterpal, N., Hanft, S., Philips, M. R., & Weissmann, G. (1998). Modes of action of aspirin-like drugs: salicylates inhibit ERK activation and integrin-dependent neutrophil adhesion. *Proceedings of the National Academy of Sciences of the United States of America, 95*(24), 14540-14545. https://doi.org/10.1073/pnas.95.24.14540

Shah, W., Hillman, T., Playford, E. D., & Hishmeh, L. (2021). Managing the long term effects of COVID-19: summary of NICE, SIGN, and RCGP rapid guideline. *BMJ, 372*, n136. https://doi.org/10.1136/bmj.n136

Spiegelenberg, J. P., van Gelder, M., Maas, M. L., Hovens, M. M. C., Esselink, A., Dofferhoff, A. S. M., … Leentjens, J. (2021). Prior use of therapeutic anticoagulation does not protect against COVID-19 related clinical outcomes in hospitalized patients: A propensity score-matched cohort study. *British Journal of Clinical Pharmacology, 87*(12), 4839-4847. https://doi.org/10.1111/bcp.14877

Tang, N., Li, D., Wang, X., & Sun, Z. (2020). Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *Journal of Thrombosis and Haemostasis, 18*(4), 844-847. https://doi.org/10.1111/jth.14768

Task Force for the management of, C.-o. t. E. S. o. C. (2022). European Society of Cardiology guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: part 1-epidemiology, pathophysiology, and diagnosis. *European Heart Journal, 43*(11), 1033-1058. https://doi.org/10.1093/eurheartj/ehab696

Testa, S., Paoletti, O., Giorgi-Pierfranceschi, M., & Pan, A. (2020). Switch from oral anticoagulants to parenteral heparin in SARS-CoV-2 hospitalized patients. *Internal and Emergency Medicine, 15*(5), 751-753. https://doi.org/10.1007/s11739-020-02331-1

Varga, Z., Flammer, A. J., Steiger, P., Haberecker, M., Andermatt, R., Zinkernagel, A. S., … Moch, H. (2020). Endothelial cell infection and endotheliitis in COVID-19. *The Lancet, 395*(10234), 1417-1418. https://doi.org/10.1016/S0140-6736(20)30937-5

Wang, L., Li, H., Gu, X., Wang, Z., Liu, S., & Chen, L. (2016). Effect of Antiplatelet Therapy on Acute Respiratory Distress Syndrome and Mortality in Critically Ill Patients: A Meta-Analysis. *PLoS One, 11*(5), e0154754.

https://doi.org/10.1371/journal.pone.0154754
World Health Organization. (2024). Number of COVID-19 cases reported to WHO. Retrieved from https://data.who.int/dashboards/covid19/cases
Yau, J. W., Teoh, H., & Verma, S. (2015). Endothelial cell control of thrombosis. *BMC Cardiovascular Disorders, 15*, 130. https://doi.org/10.1186/s12872-015-0124-z
Zaim, S., Chong, J. H., Sankaranarayanan, V., & Harky, A. (2020). COVID-19 and Multiorgan Response. *Current Problems in Cardiology, 45*(8), 100618. https://doi.org/10.1016/j.cpcardiol.2020.100618