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# Prognostic implication of uncontrolled hypertension in hospitalized patients with COVID-19

**İbrahim Halil Özdemir[a], Bülent Özlek[b], Mehmet Burak Özen[a], Ramazan Gündüz[a], Nurullah Çetin[c]**

[a] *Department of Cardiology, Manisa City Hospital, Manisa, Turkey*
[b] *Department of Cardiology, Faculty of Medicine, Mugla Sitki Kocman University, Mugla, Turkey*
[c] *Department of Cardiology, Faculty of Medicine, Celal Bayar University, Manisa, Turkey*

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SOUHRN

**Cíl:** Cílem této studie bylo zhodnotit vliv hypertenze (HT) jako kardiovaskulárního rizikového faktoru a antihypertenzní léčby na prognózu pacientů s onemocněním COVID-19.
**Metody:** Do studie bylo zařazeno celkem 117 pacientů s diagnózou onemocnění COVID-19 stanovenou testem PCR z výtěru z nosohltanu. Pacienti byli rozděleni do skupiny hypertoniků a kontrolní skupiny. Zaznamenávaly se výsledky biochemických laboratorních vyšetření, celkový krevní obraz i výsledky vyšetření zobrazovacími metodami. Hodnotila se mortalita pacientů s HT i bez tohoto onemocnění stejně jako vliv antihypertenzní léčby na mortalitu.
**Výsledky:** Vyšetření hrudníku výpočetní tomografií prokázalo statisticky významně častěji přítomnost denzity mléčného skla a konsolidace plicní tkáně ve skupině s HT ($p < 0,001$). Pobyt v nemocnici (ve dnech) byl statisticky významně delší ve skupině s HT a častěji bylo rovněž nutné přeložit pacienta na jednotku intenzivní péče ($p < 0,001$). Mortalita pacientů s HT byla vyšší než mortalita pacientů bez tohoto onemocnění ($p < 0,001$). Nebyl nalezen statisticky významný rozdíl v mortalitě skupin podle antihypertenzní léčby ($p = 0,801$).
**Závěr:** Hypertenze představuje významný rizikový faktor zvyšující mortalitu pacientů s onemocněním COVID-19. Léčba HT byla u většiny pacientů nedostatečná. Zánětlivé parametry byly zvýšené zvláště u pacientů s nedostatečně léčenou HT. U pacientů s nedostatečně léčenou HT existuje vyšší riziko úmrtí. Nejsou k dispozici žádné údaje, z nichž by bylo možno usuzovat, že by užívání inhibitorů angiotenzin konvertujícího enzymu (ACE) nebo blokátorů $AT_1$ zhoršovalo prognózu. Vysoký krevní tlak při příjmu do nemocnice je významným faktorem a probíhající antihypertenzní léčba se nesmí vysadit.



*Keywords:*
Antihypertensive treatment
Blood pressure
COVID-19
Hypertension

ABSTRACT

**Objective:** In this study, we aimed to investigate the effect of hypertension (HT) and antihypertensive treatment on prognosis, which is one of the cardiovascular risk factors affecting the prognosis of COVID-19.
**Methods:** We included 117 patients diagnosed with COVID-19 by nasopharyngeal polymerase chain reaction (PCR). The patients were divided into a hypertensive group and a control group. Biochemical, complete blood count and imaging data of the patients were recorded. Mortality of patients with and without HT was evaluated. The effect of antihypertensive therapy on mortality was evaluated.
**Results:** In thorax CT, ground glass opacity and pneumonic consolidation were found statistically significantly higher in the hypertensive group ($p < 0,001$). Hospital stay duration (days) of the patients were significantly longer in the hypertensive group and need for intensive care unit was statistically higher in the hypertensive group ($p < 0,001$). Mortality of hypertensive patients was higher than of those without hypertension ($p < 0,001$). There was no statistically significant difference in mortality in antihypertensive treatment groups ($p = 0,801$).
**Conclusion:** Hypertension is an important risk factor that increases mortality in COVID-19 patients. Uncontrolled hypertension was common in most patients. Inflammatory parameters are higher especially in patients with uncontrolled hypertension. Patients with uncontrolled hypertension have a higher risk of mortality. There is no data to suggesting that the use of ACEI/ARB worsens prognosis. High blood pressure on admission to the hospital is important and the patient's current antihypertensive therapy should not be discontinued.

**Address:** İbrahim Halil Özdemir, MD, Department of Cardiology, Manisa City Hospital, Adnan Menderes Mh. 132. Sokak No: 15 45040 Şehzadeler, Manisa, Turkey, e-mail: dr.ibrahimhalilozdemir@gmail.com
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## Introduction

On December 31st 2019 a number of unidentified cases of pneumonia were reported, with epidemiological links to the Huanan Seafood Wholesale Market in Wuhan in Hubei, China.[1] Shortly after, the Center for Disease Control and Prevention of the People's Republic of China isolated a new coronavirus as the causative agent of this epidemic, called the human epithelial cell acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] On February 12th 2020 the World Health Organization (WHO) named the disease caused by SARS-CoV-2 as the Coronavirus Disease 2019 (COVID-19). On March 11th 2020 the WHO officially announced COVID-19 to be a pandemic.[3]

The spread rate of the disease and the increase in mortality have caused all studies to focus on this issue. When mortality due to COVID-19 was examined, it was found that patients with cardiovascular risk factors were particularly affected.[4] Hypertension, diabetes mellitus, chronic obstructive pulmonary disease, atherosclerotic vascular diseases were observed more in patients with poor prognosis.[5–7] Hypertension has come to the fore due to its higher prevalence than other risk factors. In addition, opinions were made that the drugs used in the treatment of hypertension may have harmful side effects in the first period of the pandemic and treatment changes were recommended. This is because in animal studies, the ACE2 receptor was found to be a potential route for SARS-CoV-2 entry into the host cell,[8] and the most widely used drug group in the treatment of hypertension are angiotensin converting enzyme inhibitors (ACEI) / angiotensin receptor blockers (ARB).

In our study, we evaluated the clinical, laboratory, and imaging results of hypertensive COVID-19 patients in Turkey. The relationship between hypertension and mortality in COVID-19 patients and the effect of the choice of antihypertensive treatment on mortality were evaluated.

## Methods

This was a single-centered, retrospective, and observational study on adults with COVID-19 at Manisa Merkezefendi State Hospital. The data of 117 patients hospitalized between March 20th and April 20th were extracted from electronic medical records and evaluated. 117 patients diagnosed with COVID-19 by positive PCR tests (with SARS-CoV-2 [2019-nCoV] qPCR Detection Kit by Bio-Speedy) were included in our study. The patients were divided into two groups. Those with and without hypertension diagnosis. The patients' application complaints, risk factors, imaging (computed tomography [CT]) results and the antihypertensive drugs they used were recorded. Biochemical and complete blood counts of the patients were recorded. With serial troponin-I and electrocardiography follow-up, the diagnosis of acute coronary syndrome was excluded. Pulmonary embolism causing high D-dimer levels was excluded by computed tomography. Biochemical data, imaging results, and mortality of the two groups were compared. Hypertensive drugs were divided into two groups. ACEI/ARB users and others (aldosterone antagonists, beta blockers, calcium channel blockers, diuretics, alpha blockers). Mortality data of these two groups were compared.

Ministry of Health of the Republic of Turkey gave approval for the study. The research protocol complied with the Declaration of Helsinki and was approved by Celal Bayar University Medical Faculty Non-Interventional Clinical Trials Ethics Committee (Decision No: 85252386-050.04.04.04-).

### *Statistical analysis*

In calculating the sample of this study conducted for "Prognostic implication of uncontrolled hypertension in hospitalized patients with COVID-19", power was determined by taking at least 0.80 and 1st type error as 0.05 for each variable. The continuous (numeric) variables were presented by descriptive statistics such as mean and standard deviation; whereas the categorical variables were presented by numbers and percentages. The Kolmogorov–Smirnov test was used to check whether the continuous variables showed normal distribution (n >50), and nonparametric tests were used for analysis, as the variables did not show normal distribution. The Mann–Whitney U test was used to compare the measurements by groups. We used the Kruskal–Wallis H test to compare the "CRP and D-dimer measurements" according to the "CT result" and the "hospitalization times" according to the "antihypertensive treatment" and the Bonferroni post-hoc (multiple) comparison tests to determine the different groups. We used the Chi-squared test to determine the correlations between categorical variables. Statistical significance level was set at ($\alpha$) 5%, and SPSS (IBM SPSS for Windows, Ver. 24) package software was used for calculations.

## Results

Hypertension group consisted of 46 patients, control group consisted of 71 patients. There was no statistically significant difference in age, female gender, smoking, alcohol use and body mass index between the groups. Systolic blood pressure ($p$: 0.05) and diastolic blood pressure ($p$ <0.001) were statistically higher in the hypertensive group. The symptoms of fever, cough and shortness of breath were statistically significantly higher in the hypertensive group ($p$ <0.001). Cough (80.4%) was the most common symptom in the hypertensive group. There was no statistically significant difference between the two groups in terms of other risk factors (diabetes mellitus, anemia, renal failure, coronary artery disease, peripheral vascular disease, chronic heart failure, hyperlipidemia, chronic obstructive pulmonary disease). In thorax CT, ground glass opacity, and pneumonic consolidation were found statistically significantly higher in the hypertensive group ($p$ <0.001). Hospital stay duration (days) of the patients was significantly longer in the hypertensive group and the need for intensive care unit was statistically higher in the hypertensive group ($p$ <0.001) (Table 1). Mortality of hypertensive patients was higher than of those without hypertension ($p$ <0.001) (Table 1).

D-dimer ($p$ <0.001), troponin-I ($p$ <0.001), CRP ($p$: 0.032) and neutrophil/lymphocyte ratio (NLR) ($p$: 0.049) were statistically significantly higher in the hypertensive

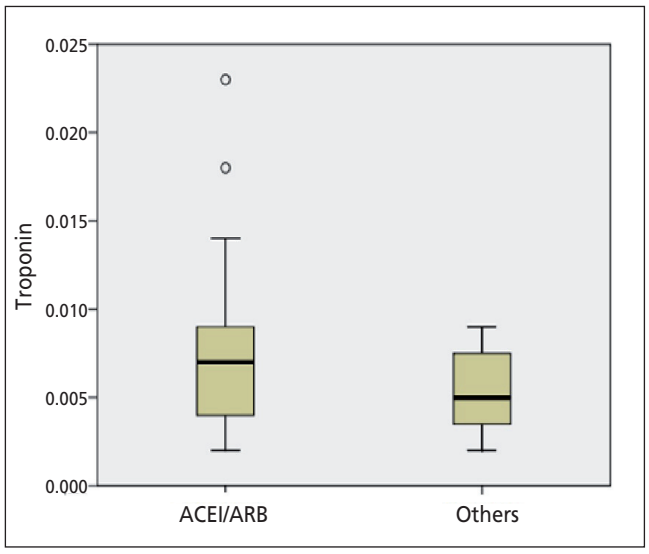


**Fig. 1 – Troponin I levels in antihypertensive groups.**

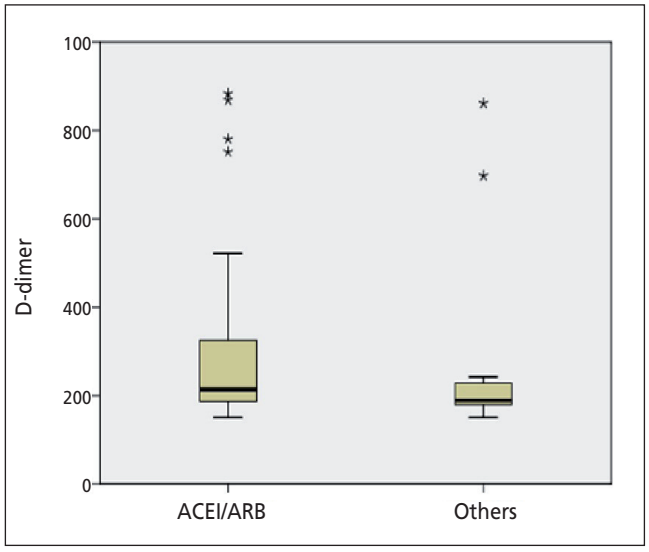


**Fig. 2 – D-dimer levels in antihypertensive groups.**

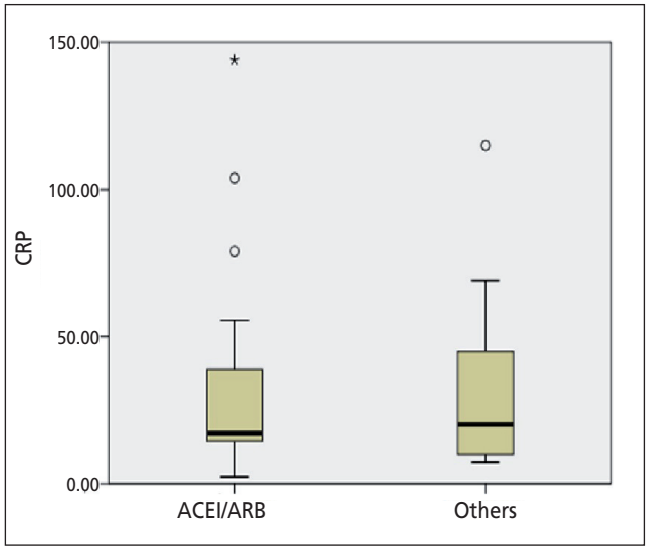


**Fig. 3 – CRP levels in antihypertensive groups.**

**Table 1 – Baseline characteristics of study population**

| | Patients with hypertension (n = 46) | Patients without hypertension (n = 71) | *p*-value |
|---|---|---|---|
| Age, years | 50.86±24.6 | 49.65±18.1 | 0.113 |
| Female sex, n (%) | 21 (45.6) | 33 (46.4) | 0.412 |
| Smoking, n (%) | 12 (26.1) | 20 (28.2) | 0.556 |
| Alcohol use, n (%) | 4 (8.7) | 7 (9.8) | 0.341 |
| Body mass index, kg/m$^2$ | 28.9±2.3 | 29.4±1.9 | 0.267 |
| Systolic blood pressure, mm Hg | 165±20 | 130±15 | **0.050** |
| Diastolic blood pressure, mm Hg | 95±15 | 70±10 | **<0.001** |
| Heart rate, bpm | 86±26 | 79±32 | 0.118 |
| **Symptoms at admission, n (%)** | | | |
| Fever | 35 (76.1) | 41 (57.7) | **<0.001** |
| Cough | 37 (80.4) | 36 (50.7) | **<0.001** |
| Shortness of breath | 16 (34.8) | 11 (15.5) | **<0.001** |
| Headache | 4 (8.7) | 6 (8.5) | 0.449 |
| Diarrhea | 2 (4.3) | 4 (5.6) | 0.387 |
| Fatigue, tiredness | 6 (13) | 9 (12.7) | 0.348 |
| Muscle ache | 9 (19.6) | 12 (16.9) | 0.229 |
| Sore throat | 8 (17.4) | 12 (16.9) | 0.203 |
| Chest pain | 1 (2.2) | 2 (2.8) | 0.184 |
| **Comorbidities, n (%)** | | | |
| Diabetes mellitus | 6 (13) | 9 (12.7) | 0.348 |
| Anemia | 2 (4.3) | 4 (5.6) | 0.387 |
| Renal failure | 4 (8.7) | 7 (9.8) | 0.477 |
| Dialysis | 0 | 0 | – |
| Coronary artery disease | 3 (6.5) | 5 (7) | 0.324 |
| PCI/CABG | 1 (2.2) | 3 (4.2) | 0.275 |
| Peripheral vascular disease | 1 (2.2) | 2 (2.8) | 0.184 |
| Chronic heart failure (HFrEF) | 1 (2.2) | 2 (2.8) | 0.184 |
| Hyperlipidemia | 3 (6.5) | 5 (7) | 0.324 |
| Chronic obstructive pulmonary disease | 3 (6.5) | 7 (9.8) | 0.498 |
| **Thorax CT findings, n (%)** | | | |
| No significant finding | 6 (13) | 38 (53.5) | **<0.001** |
| Ground glass opacity | 36 (78.3) | 31 (43.7) | <0.001 |
| Pneumonic consolidation | 4 (8.7) | 2 (2.8) | **<0.001** |
| Need for intensive care unit, n (%) | 29 (63) | 21 (29.6) | **<0.001** |
| Hospital stay duration (days) | 10.94±2.83 | 8.14±2.48 | **<0.001** |
| Mortality, n (%) | 17 (36.9) | 9 (12.7) | **<0.001** |

±SD – standard deviation.
CABG – coronary artery bypass graft; CT – computed tomography; HFrEF – heart failure with reduced ejection fraction; PCI – percutaneous coronary intervention.

**Table 2 – Laboratory data of population**

| | Patients with hypertension (n = 46) | Patients without hypertension (n = 71) | *p*-value |
|---|---|---|---|
| Urea, mg/dL | 52±17 | 69±22 | 0.345 |
| Serum creatinine, mg/dL | 1.12±0.62 | 1.23±0.54 | 0.089 |
| Serum potassium, mmol/L | 3.8±0.6 | 4.1±0.4 | 0.402 |
| Serum calcium, mg/dL | 9.2±0.3 | 9.0±0.6 | 0.399 |
| Uric acid, mg/dL | 5.6±2.8 | 6.8±1.9 | 0.585 |
| Albumin, g/dL | 4.1±0.3 | 4.3±0.2 | 0.341 |
| Aspartate transaminase, u/L | 32±11 | 21±20 | 0.246 |
| Alanine transaminase, u/L | 27±16 | 22±17 | 0.281 |
| D-dimer, ng/mL | 309.98±229.44 | 180.27±82.84 | **<0.001** |
| Troponin, ng/mL | 0.012±0.04 | 0.003±0.00 | **<0.001** |
| Ferritin, ng/mL | 92.49±106.29 | 60.91±54.93 | 0.276 |
| Hemoglobin, g/dL | 11.8±1.4 | 11.3±1.2 | 0.181 |
| Leukocyte, × $10^3$/µL | 6.71±3.04 | 6.43±2.27 | 0.886 |
| Lymphocyte, × $10^3$/µL | 1.44±0.86 | 1.56±0.98 | 0.143 |
| C-reactive protein (CRP), mg/L | 32.37±32.01 | 28.18±23.8 | **0.032** |
| Neutrophil/lymhocyte ratio (NLR), (uL) | 3.65±1.86 | 3.12±2.11 | **0.049** |

±SD – standard deviation.

**Table 3 – Comparison of laboratory data and mortality of ACEI/ARB and other antihypertensive drugs groups**

| | ACEI/ARB (n = 32) | Other antihypertensive drugs (n = 14) | *p*-value |
|---|---|---|---|
| C-reactive protein (CRP), mg/L | 31.12±32.03 | 35.52±33.28 | 0.743 |
| D-dimer, ng/mL | 315.92±227.81 | 294.81±244.06 | 0.341 |
| Troponin-I, ng/mL | 0.015±0.004 | 0.011±0.003 | 0.187 |
| Neutrophil/lymphocyte ratio (NLR), uL | 3.59±1.61 | 3.68±1.53 | 0.264 |
| Mortality, n (%) | 12 (37.5) | 5 (35.7) | 0.801 |

±SD – standard deviation.

group. There was no statistically significant difference between the two groups in other parameters (urea, serum creatinine, serum potassium, serum calcium, uric acid, albumin, aspartate transaminase, alanine transaminase, ferritin, hemoglobin, leukocyte, lymphocyte) (Table 2).

Hypertensive patients mostly used angiotensin converting enzyme inhibitor (ACEI) / angiotensin II receptor blockers (ARB) class drugs (69.6%). There was no statistically significant difference in mortality in antihypertensive treatment groups (*p*: 0.801) (Table 3).

There was no statistically significant difference in troponin I (*p*: 0.187) (Fig. 1), D-dimer (*p*: 0.341) (Fig. 2), CRP (*p*: 0.743) (Fig. 3) and NLR (p: 0.264) levels between antihypertensive treatment groups (Table 3).

## Discussion

The number of patients infected with COVID-19 is growing rapidly worldwide. COVID-19 is detected in all age groups. Studies have shown that mortality increases with increasing age. The reason for this is thought to be that cardiovascular risk factors increase with increasing age. Guan et al. on 1099 COVID-19 cases in China reported hypertension to be observed in 15% of all cases, in 24% of severe cases, and 13% of mild cases.[9] The most common risk factor seen in our patients was hypertension (39.3%). It suggests that patients with hypertension experience more severe COVID-19. In our study, we found that hypertensive patients had longer hospitalization and treatment periods. Most of the patients in need of intensive care had hypertension. The mortality of hypertensive patients was statistically higher.

In the initial stage of the COVID-19 outbreak, patients were admitted to the hospital with atypical viral symptoms. Among the symptoms, cough and fever were the most common. Symptoms such as fever, cough, and shortness of breath were statistically higher in the hypertensive patient group. The clinical symptoms of the non-hypertensive patient group were more atypical. This situation seems to be related to the more serious clinical presentation of the hypertensive group. The most important involvement determining the COVID-19 mortality is respiratory system involvement and the pulmonary lesion (ground glass opacity and pneumonic consolidation) was observed higher in the hypertensive group in thorax CT. CT findings have been reported in correlation with the prognosis of patients.[10] In this study, evaluation of CT results of all patients concluded that CRP and D-dimer levels in GGO patients were significantly higher than those without. We found significantly higher D-dimer levels in patients with hypertension than those who did not suffer from hypertension. D-dimer levels correlate with the severity of the disease.[11] Intermittent D-Dimer can be followed for prognosis.

Matsumoto et al. reported that the CRP levels revealed a positive correlation with the severity of lung disease.[12] Higher CRP levels are associated with the severity of inflammation and are not affected by age, gender, or physical condition.[13] The CRP levels were significantly higher in hypertensive patients compared to others. CRP levels are thought to vary depending on the course of pulmonary disease. Measuring and monitoring CRP levels in the early stages can help to appreciate the severity of the course of COVID-19. Another value that indicates the patient's inflammatory status is neutrophil lymphocyte ratio (NLR).[14] Qin et al. reported severe COVID-19 cases to have higher neutrophil counts but lower lymphocyte counts compared to non-severe cases, suggesting that NLR tends to be higher in patients with severe infection.[15] The NLR levels of our hypertensive patients were significantly higher as well. The inflammatory response is impaired in COVID-19 patients. COVID-19 induced neutrophil production and lymphocyte apoptosis may accelerate. An increase in neutrophil count and a decrease in lymphocyte count were observed in Middle East respiratory syndrome coronavirus (MERS-CoV) infected patients, which were similar to the SARS-CoV-2 virus. This change is

remarkable especially in patients who died due to MERS-CoV.[16,17] Since NLR can be quickly calculated, clinicians can identify high-risk COVID-19 patients at early stages. In hypertensive patients diagnosed with COVID-19, it can provide valuable information about the severity of the inflammation process. It is safe to assume that it would be lower in early stage COVID-19 patients.

It is known that there is a relationship between inflammation and blood pressure. Studies have shown that the increase in inflammatory markers has an increased effect on blood pressure.[18,19] It causes endothelial dysfunction due to high blood pressure.[20] Vascular endothelial function is closely related to inflammation.[21] The synergistic effect of high blood pressure and inflammation may increase endothelial dysfunction. In a study found that the interactions between inflammatory markers and blood pressure had an effect on hospital outcome.[22] It was found that the blood pressure of the patients during the first admission to the emergency service was higher in the hypertensive patient group. High blood pressure and increased inflammatory mediators in the hypertensive patient group may have contributed to the increase in endothelial dysfunction. Endothelial dysfunction has been shown to be associated with microvascular thrombosis and prothrombotic state in COVID-19 patients.[23] With the prothrombotic effect, hypertensive patients need higher mean blood pressure levels for perfusion of vital organs than normotensive patients.

Troponin-I levels have been reported to be a strong indicator of prognosis in COVID-19 patients. It was observed that troponin-I levels of patients who were followed up in intensive care unit due to severe COVID-19 were higher than of patients with mild clinical course.[24] High troponin-I levels were detected in our hypertensive patients. Our hypertensive patients did not have a history of coronary artery disease or cardiomyopathy. In patients with serial angina, electrocardiography, and troponin-I follow-up, there was no evidence of acute coronary syndrome, but an increase in mild and non-progressive troponin-I levels was observed in hypertensive patients. Direct (not coronary) myocardial injury appears to be the most common mechanism due to viral myocarditis or systemic inflammation. We observed higher troponin-I levels, especially in hypertensive patients with high mortality. Aggressive treatment may be considered for patients at high risk of myocardial ischemia.

Antihypertensive treatments were held responsible for the high mortality rate of hypertensive patients. During the early stages of the outbreak, Lei Fang et al. reported that CCB should be preferred instead of ACEI or ARB in COVID-19 patients due to the increase of worsened clinical outcomes.[25] The hypothesis behind this recommendation was that the entry point of the SARS-CoV-2 was the ACE2 receptor and that ACEIs and ARBs had the potential to upregulate ACE2. Thereupon, some medical centers have proposed to stop the use of renin-angiotensin system (RAS) inhibitors. With increasing experience on COVID-19 and obtaining more patient data, this proposal turned out to be wrong. Studies show that daily intake of antihypertensive medications by COVID-19 patients should not be discontinued and ACEI/ARB class drugs may have mortality-reducing effects.[26,27] In our study, no relation was found between antihypertensive drug type and mortality. We did not find any difference according to the antihypertensive treatment type in terms of CRP, troponin-I, D-dimer levels which we evaluated as a prognosis indicator in hypertensive patients. In a meta-analysis including 27 studies; the exposure to ACEI/ARB did not increase the risk of all-cause mortality among patients with COVID-19.[28] Conversely, exploratory analysis in studies involving hypertensive patients showed an association between ACEI/ARB and a significant reduction in mortality risk. In another meta-analysis that included 59 studies, use of an ACEI/ARB in COVID-19 patients was significantly associated with lower odds or hazard of mortality compared with non-use of ACEI/ARB.[29] In another study analyzing 4069 patients with laboratory-confirmed SARS-CoV-2 infection and hospitalized at 34 clinical centers, the use of neither ACE-I nor ARB was associated with mortality.[30] It seems wise to continue the current antihypertensive treatment that keeps blood pressure under control following the recommendations of international scientific communities (e.g. the European Society of Cardiology, Hypertension Canada, The Canadian Cardiovascular Society, UK Renal Association and the International Society of Hypertension).

### *Study limitations*

This study has several limitations. First, the number of patients included in the study is low. Second, ACEI/ARB was considered as a group, so it did not have the power to detect if there was a different effect between ACEI and ARB. Third, since the retrospective nature of this study, some parameters were not available in all patients, and in-hospital medications might be not fully recorded.

## Conclusion

Considering its rapid clinical course, the risk factors of COVID-19 need to be evaluated at initial hospital admission as soon as possible. Hypertension per se is not a risk factor for COVID-19. The hypertensive patients had higher inflammatory markers and longer hospitalizations compared to patients with other risk factors. One may conclude that hypertension should be given particular attention in initial evaluation. Uncontrolled hypertension was common in most patients. Inflammatory parameters are higher especially in patients with uncontrolled hypertension. CRP and D-dimer levels both seem to be especially crucial in the follow-up. The patients with uncontrolled hypertension have a higher risk of mortality. It should be kept in mind that all patients may have mildly elevated troponin-I levels, which is more likely to be related to viral myocardial damage rather than acute coronary syndrome. There is no data to suggest that the use of ACEI/ARB worsens prognosis.

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**Author contributions**
Idea/concept: İ. H. Özdemir, N. Çetin; design: İ. H. Özdemir, M. B. Özen, R. Gündüz; data collection/processing: R. Gündüz, M. B. Özen; analysis/interpretation: İ. H. Özdemir, N. Çetin; literature review: M. B. Özen, R. Gündüz; drafting/writing: İ. H. Özdemir, N. Çetin; critical review: İ. H. Özdemir, M. B. Özen

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