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Does COVID-19 Cause Hypertension?

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Abstract

The coronavirus disease 2019 (COVID-19) outbreak remains a major public health challenge worldwide. The present study investigated the effect of COVID-19 on blood pressure (BP) during short term follow-up. A total of 211 consecutive COVID-19 patients who were admitted to Parkhayat Kutahya hospital were retrospectively screened. Information was obtained from the electronic medical records and National health data registry. The study outcome was new onset of hypertension according to the Eight Joint National Committee and European Society of Cardiology Guidelines. Finally, 153 confirmed COVID-19 patients (mean age 46.5 ± 12.7 years) were enrolled. Both systolic (120.9 ± 7.2 vs 126.5 ± 15.0 mmHg, P <.001) and diastolic BP (78.5 ± 4.4 vs 81.8 ± 7.4 mmHg, P <.001) were significantly higher in the post COVID-19 period than on admission. New onset hypertension was observed in 18 patients at the end of 31.6 ± 5.0 days on average (P <.001). These findings suggest that COVID-19 increases systolic and diastolic BP and may cause new onset hypertension.

Keywords

COVID-19, hypertension, pandemic, angiotensin

Introduction

The coronavirus disease 2019 (COVID-19) outbreak remains a major public health challenge worldwide. COVID-19 disease is caused by a novel coronavirus: severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] The number of new cases continues to increase and >4 million people died due to the COVID-19 pandemic.[2] With the growing understanding of the pathophysiology of this disease and its effect on multiple systems, various comorbidities were investigated.[3] The post COVID-19 infection period should also be investigated in order to identify the short-, mid-, and long-term adverse outcomes and new onset comorbidities that may develop.

Hypertension is associated with an increased risk of severe COVID-19 and higher mortality rate in these patients.[4] However, the effect of COVID-19 on blood pressure (BP) has not yet been elucidated. Therefore, the present study aimed to investigate the effect of COVID-19 on BP and change in the prevalence of hypertension in COVID-19 patients.

Methods

In the present retrospective cohort study, a total of 211 consecutive COVID-19 patients who admitted to Parkhayat Kutahya hospital from December 15, 2020 to April 01, 2021 were screened. The following patients were excluded: those under the age of 18, who received steroid therapy, with systemic inflammatory disease history, previous kidney or liver failure history, with hypertension, who left the follow-up and with missing data. Finally, 153 eligible patients (75%) were analyzed (Figure 1).

The diagnosis of COVID-19 was confirmed by the detection of the presence of SARS-CoV-2 ribonucleic acid on an oropharyngeal and nasopharyngeal swab using reverse transcriptase polymerase chain reaction in the Public Health Microbiology Laboratory of the Ministry of Health according to World Health Organization guidance.[5] Oropharyngeal and nasopharyngeal swabs were collected at the time of admission to the outpatient unit.

The study outcome was new onset hypertension. New onset hypertension was defined as values ≥140 mmHg systolic BP and/or ≥90 mmHg diastolic BP in office measurements and ≥135 mmHg systolic BP and/or ≥85 mmHg diastolic BP in home BP monitoring according to Eighth Joint National Committee (JNC 8) and European Society of Cardiology guidelines.[6,7] In the COVID-19 unit, BP was measured 3 times on the right upper-arm in the seated position by a trained nurse using a sphygmomanometer after 15 min resting. The average of the 3 measurements was used. Proper cuff size was determined based on arm circumference. The measurement was performed under controlled condition in a quiet room.

The patient characteristics, laboratory results, treatment protocol and outcome data of patients were obtained from the electronic medical records of Parkhayat Kutahya hospital and National health data registry (e-Nabız®). For all patients,

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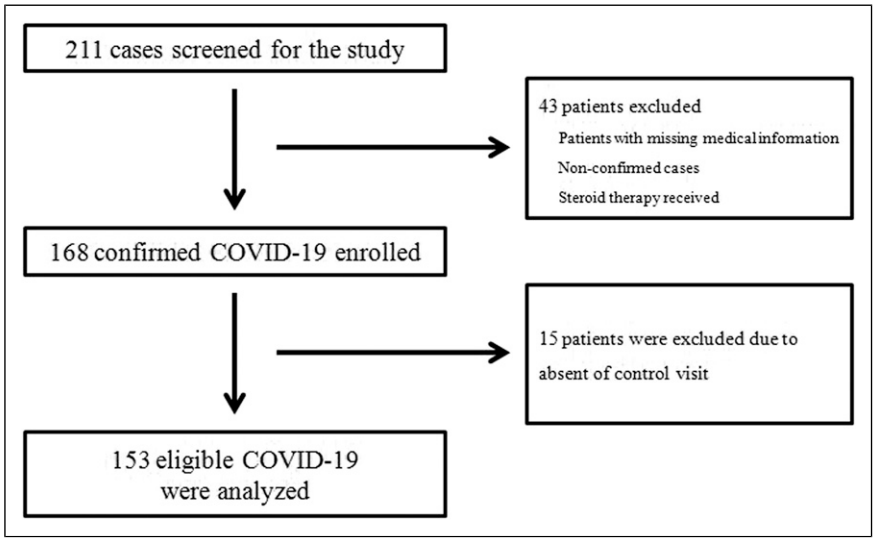

Figure 1. Study participants.

blood samples for routine laboratory analysis were drawn upon admission and follow-up in the COVID-19 outpatient unit. Laboratory analyses were performed in the laboratories of Parkhayat Kutahya hospital.

Complete blood count was measured with ELite 580 advanced hematology analyzer (Erba, Czech Republic). C-reactive protein, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatinine were measured by Beckman Coulter AU 640 (Japan) analyzer. Ferritin and high sensitive troponin-I (HsTrop-I) were measured by Beckman Coulter DXI 800 (Japan) analyzer. D-dimer was determined with the Getein 1600 immunofluorescence quantitative analyzes (China). Bio-Speedy® SARS-CoV-2 (2019-nCoV) qPCR Detection Kits (Bioeksen, Istanbul, Turkey) were used to detect COVID-19. Repeatability of the kit is 100% and the reproducibility combined with the robotic extraction is 100% at concentrations over the LOD (Limit of detection). LOD for all the sample types is 20 genomes/mL. Sensitivity and specificity of the Bio-Speedy® kit were 99.4–99.0%, respectively.[8]

The management of the treatment protocol for COVID-19 was left to the discretion of the pandemic team consisting of infection disease, radiology, chest disease, anesthesiology, cardiology, and internal medicine specialized medical doctors and pharmacists as recommended by updated guideline by the Turkish Ministry of Health. The present study was approved by the institutional review board (Protocol no: E-41997688-050.99-8877) and the Republic of Turkey Ministry of Health.

Table 1. Baseline characteristics.

	n = 153
Age, years	46.5 ± 12.7
Female, n (%)	101 (66%)
Body mass index, kg/m^2	25.8 ± 4.4
Symptoms on admission	
Fever, n (%)	75 (49)
Sore throat, n (%)	64 (42)
Fatigue, n (%)	113 (74)
Cough, n (%)	100 (65)
Hyposmia, dysosmia, or anosmia, n (%)	26 (17)
Headache, n (%)	10 (7)
Dyspnea, n (%)	60 (39)
Myalgia, n (%)	59 (39)
Diarrhea, n (%)	5 (3)
Medications	
Favipiravir, n (%)	120 (78)
Chloroquine/hydroxychloroquine, n (%)	117 (77)
Azithromycin, n (%)	49 (32)
Anti-coagulant use, n (%)	58 (38)
Steroid, n (%)	0 (0)
High dose of steroid, n (%)	0 (0)
Tocilizumab, n (%)	0 (0)
Follow-up time, days	31.6 ± 5.0
In-hospital follow-up, n (%)	8 (5)
Hospital stay, days	6.1 ± 1.0

Statistical Analysis

Continuous variables were tested for normal distribution by the Kolmogorov–Smirnov test. The variables are expressed as means ± standard deviation or median (interquartile range). Dependent continuous variables were compared with paired sample t-tests or Wilcoxon signed rank tests, as appropriate. Dependent categorical variables were compared with McNemar's test. We performed a power analyses according to changes in systolic and diastolic BP by the follow-up period and found a power of >.98 (P = 1-β error probability) for both. The power analyses for new onset hypertension as a dependent categorical variable was .88 (P = 1-β error probability). A two-tailed P <.05 was considered significant. All statistical analyses were performed

Table 2. Clinical characteristics and laboratory findings.

	On admission of COVID-19	Post COVID-19	*P*
Laboratory findings			
Hemoglobin, g/dL	13.5 ± 1.8	13.6 ± 1.6	.728
White blood cells, $10^3/\mu L$	5.1 ± 1.6	5.3 ± 1.5	.224
Lymphocytes, $10^3/\mu L$	1.5 ± 1.6	1.5 ± 0.5	.272
C-reactive protein, mg/L	5.0 (2.0–10.4)	3.0 (2.0–5.0)	<.001
High sensitive troponin-I, pg/mL	9.6 ± 6.4	3.8 ± 3.4	<.001
D-Dimer, ng/mL	149.0 (100.0–300.0)	119.9 (100.0–187.7)	<.001
Ferritin, ng/mL	49.0 (18.1–97.7)	49.0 (23.0–97.7)	.058
Lactate dehydrogenase, U/L	166.0 ± 73.1	154.2 ± 46.6	.514
Creatinine, mg/dL	.92 ± .20	.92 ± .16	.611
Alanine aminotransferase, U/L	30.5 ± 22.1	29.0 ± 19.8	.754
Aspartate aminotransferase, U/L	30.4 ± 14.5	27.8 ± 8.8	.409
Systolic blood pressure, mmHg	120.9 ± 7.2	126.5 ± 15.0	<.001
Diastolic blood pressure, mmHg	78.5 ± 4.4	81.8 ± 7.4	<.001
Previous medical history			
Hypertension, n (%)	0 (0)	18 (12)	<.001
Diabetes mellitus, n (%)	16 (11)	19 (12)	.375
Coronary artery disease, n (%)	6 (4)	8 (5)	.500
Chronic obstructive pulmonary disease, n (%)	10 (7)	14 (9)	.125

using the SPSS statistical package for Windows version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 153 confirmed COVID-19 patients (mean age 46.5 ± 12.7 years) were enrolled; 101 patients (66%) were female. Table 1 shows the baseline characteristics of the study population. Body mass index was 25.8 ± 4.4. The common symptoms were fatigue, cough, and fever (74%, 65% and 49%, respectively). Sore throat was seen in 42% of patients while dyspnea was seen in 39% and myalgia was seen in 39% of the study population. Hyposmia, dysosmia, anosmia, headache and diarrhea were rare symptoms on admission in patients with COVID-19. Favipiravir and chloroquine/hydroxychloroquine were the most given drugs (78% and 77%, respectively). Anticoagulants were administered for 38% of patients. Only 8 patients (5%) were hospitalized. Mean hospitalization time was 6.1 ± 1.0 days. Mean follow-up time was 31.6 ± 5.0 days.

Clinical characteristics and laboratory findings are shown in Table 2. There was no significant difference in hemoglobin, white blood cell, and lymphocyte count on admission and after COVID-19 (P = .728, P = .224, P = .272, respectively). The serum CRP level (5.0 (2.0–10.4) vs 3.0 (2.0–5.0) mg/L, P <.001) and D-dimer level (149.0 (100.0–300.0) vs 119.9 (100.0–187.7) ng/mL, P <.001) were significantly higher on admission than in post COVID-19 period. High sensitive troponin-I significantly decreased in the post COVID-19 period (9.6 ± 6.4 vs 3.8 ± 3.4 pg/mL, P <.001). Ferritin, lactate dehydrogenase, creatinine, and transaminases levels were not significantly different between on admission and the post COVID-19 period. New onset hypertension was observed in 18 patients (12%) during post COVID-19 period (P <.001), while diabetes mellitus, coronary artery disease, and chronic obstructive pulmonary disease were not significantly different between admission and post COVID-19 period (P = .375, P = .500 and P = .125, respectively). Both systolic (120.9 ± 7.2 vs 126.5 ± 15.0 mmHg, P <.001) and diastolic BP (78.5 ± 4.4 vs 81.8 ± 7.4 mmHg, P <.001) were significantly higher in the post COVID-19 period when compared with on admission (Figure 2).

Discussion

Since the outbreak of COVID-19 was recognized, there have been 188,650,179 confirmed cases and >4,000,000 deaths, reported to the WHO.[2] Since the pandemic started, published research focused on evaluating the optimal treatment to reduce COVID-19 mortality. Recent studies also focused on the determination of independent predictors of mortality in patients with COVID-19.[9] However, data about outcomes in post COVID-19 short- and long-term follow-up period is limited. Therefore, the present study was designed to evaluate the effect of COVID-19 on hypertension in the short term post COVID-19 period. In the present study, 153 eligible COVID-19 patients enrolled and followed up 31.6 days on average. At the end of this period, systolic and diastolic BP was significantly increased. The incidence of new hypertension was also increased.

Various biomarkers and comorbidities have been identified as independent predictors of severe disease and adverse outcomes in COVID-19.[10-12] With respect to hypertension, its

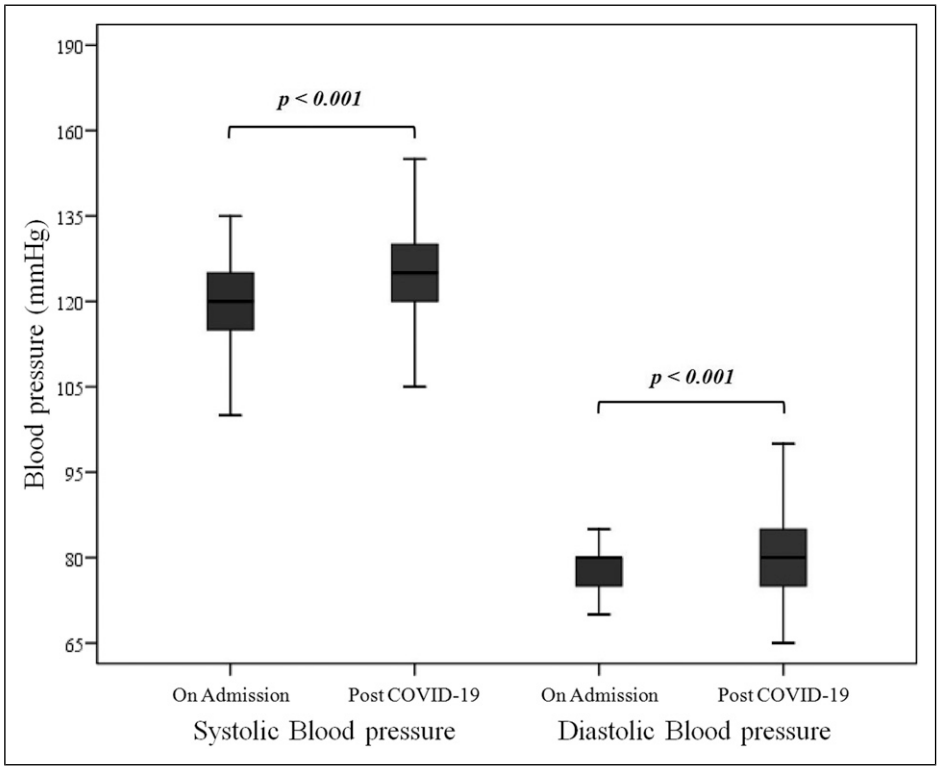

Figure 2. Systolic and diastolic blood pressure on admission and post COVID-19 period.

relation with COVID-19 has been discussed since the early stages of the pandemic. In a review by Tadic et al, a search of 14 studies was performed to determine the relationship between hypertension and COVID-19 and the role of hypertension on outcome in these patients. Tadic et al concluded that arterial hypertension represented one of the most common comorbidities in patients with COVID-19.[13] Due to the role of angiotensin converting enzyme (ACE) 2 in SARS-CoV-2 infection, it was suggested that hypertension may be involved in the pathogenesis of COVID-19.[13] In a recent study, Lippi et al found that hypertension is associated with a 2.5-fold increased risk of both increased disease severity and mortality in COVID-19 patients. They also showed that this effect was mainly observed in older patients (age >60 years).[4] On the other hand, ACE 2, as a receptor for SARS-CoV-2, is increased in the use of ACE inhibitors or angiotensin (ANG) receptor blockers. Concerns have been raised over the risk of SARS-CoV-2 infection and poor prognosis of COVID-19 in patients who are on these drugs. Various studies focused on this issue.[14,15] A review of 16 studies showed that the evidence does not suggest higher risks for SARS-CoV-2 infection or poor prognosis for COVID-19 patients treated with renin angiotensin aldosterone system (RAAS) inhibitors.[16] The American Heart Association and European Society for Cardiology confirmed this issue.[17,18]

The RAAS plays a key role in the cardiovascular system.[19] It is well known that the hyperactivation of RAAS and increases in ANG 2 levels are related with adverse outcomes (via the ANG 1 receptors) in cardiovascular diseases including heart failure, hypertension, myocardial infarction, and diabetic cardiovascular complications.[20] On the other hand, ACE 2 is an enzyme has a negative regulator role in RAAS activation mainly by converting ANG 1 and ANG 2 into ANG 1–9 and ANG 1–7, respectively. There is a balance between the protective arm ACE 2/ANG 1–7/Mas receptor axis and pathogenic arm ACE/ANG 2/ANG 2 receptor type 1 receptor axis.[21] ACE 2 is also the cellular receptor for the SARS-CoV-2 that is responsible the infectivity of COVID-19. ACE 2 is widely expressed in the cardiovascular system and in the lung, as well. Considering that ACE 2 plays a negative role in RAAS, a decrease in the ACE 2 and an increase in the ANG 2 level may lead to increase in BP. In a cohort study circulating, ANG 2 levels were significantly elevated in COVID-19 patients when compared with healthy individuals and increase of ANG 2 was linearly correlated with virus load.[22] Therefore, a direct link between ACE 2 down regulation and systemic RAAS imbalance may lead to increase ANG 2 levels and BP. Accordingly, the present study showed that both systolic and diastolic BP were significantly increased in COVID-19 patients in short term follow-up period. The new onset hypertension was observed in 18 patients at the end of the follow-up period.

The effect of COVID-19 on BP has not been elucidated yet. However, few cases of hypertension after mRNA-based

vaccination for COVID-19 have been reported. Athyros et al[23] reported a hypertensive crisis with intracranial hemorrhage 3 days after anti–COVID-19 vaccination. In a case series, Meylan et al[24] shared their 1-month experience in their vaccination center. They identified 9 patients with stage 3 hypertension after vaccination. In both reports,[23,24] the authors stated that the underlying mechanism was uncertain. An analogy may be coagulopathy which can occur both during COVID-19 infection and after vaccination. Hematological and thromboembolic events were observed after first doses of mRNA vaccines. The risks of such events were higher and more prolonged after SARS-CoV-2 infection than after vaccination.[25] The rise in BP after COVID-19 is also indirectly supported by the hypertension occurring after vaccination. More research is needed in order to confirm the occurrence of hypertension after mRNA-based vaccination and SARS-CoV-2 infection.

Stress and anxiety are the main reasons for white coat hypertension (WCH). In the present study, WCH was unlikely to affect the results because of several reasons. First, in the study population, stress or anxiety due to possible diagnosis of COVID-19 would be likely to be higher on admission. In the control visit, however, the patients knew that they had recovered from COVID-19 disease and therefore were likely to be in a better psychological condition. Despite better psychological status, both systolic and diastolic BP were significantly higher in the post COVID-19 period. Second, the first measurements and second measurements of BP were compared in the same patient. This, to some extent compensates for an anxious personality. In other words, if present, anxiety could be seen in the first as well as in the second measurement. Third, BP measurement was performed in a quiet room before the nasopharyngeal and blood sample collections. Therefore, no uncomfortable/painful procedure was applied before BP measurement. The present study has some limitations. First, the follow-up period was short. Further studies should be planned in order to investigate whether the causative effect of COVID-19 on hypertension is not evident after long term follow-up. Second, the results of the present study should be supported by the detection of biomarkers, including ANG 2 and ACE 2 levels. Third, the present study was a single-center experience and represents a small number of patients. However, our study population of unselected COVID-19 patients mirrors the real world scenario.

In conclusion, the present study showed that COVID-19 leads to increase both systolic and diastolic BP and causes new onset hypertension. The clinical implication of the present study is that, physicians should be aware of the potentially risk for new onset hypertension during the post COVID-19 period and take early action.

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Declaration of Conflicting Interests

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