



ARTERIAL HYPERTENSION FOLLOWING COVID-19: A RETROSPECTIVE STUDY OF PATIENTS IN A CENTRAL EUROPEAN TERTIARY CARE CENTER

Điđi Delalić¹, Juraj Jug² and Ingrid Prkačin^{1,3}

¹Medical School, University of Zagreb, Zagreb, Croatia;

²Health Center Zagreb West;

³Merkur University Hospital, Zagreb, Croatia

SUMMARY – The aim of this study was to determine the frequency of newly verified or worsened existing hypertension in patients who had coronavirus 2019 (COVID-19).

To be categorized as a COVID-19 patient, a positive reverse-transcription polymerase chain reaction test at a single point in time was required. The patients' age, history, laboratory values and antihypertensive therapy of patients were recorded.

In one year, 32 of 199 patients studied had either newly verified (15) or worsened existing (17) arterial hypertension. Among those patients, the median time from a verified infection to the onset of symptoms was 3 months. When the patients were divided into groups, 4 were in the acute, 11 in the sub-acute, 8 in the chronic and 9 in the "long COVID" group. Compared to the rest of the study population, patients presenting with arterial hypertension had significantly higher systolic (median 141 mmHg vs 130 mmHg, $p < 0.001$) and diastolic (median 93 mmHg vs 80 mmHg, $p < 0.001$) blood pressure and were significantly younger (median 51 vs 59 years, $p = 0.032$).

Arterial hypertension following COVID-19, either newly verified or worsened existing, is a relatively common occurrence (16% of our patient pool), indicating that more effort should be directed at evaluating the blood pressure values of patients following COVID-19.

Keywords: arterial *hypertension*, *COVID-19 infection*, *post-Covid*

Introduction

Deep into the second year of the pandemic, having made great advancements in the diagnosis and treatment of coronavirus 2019 (COVID-19) in both outpatient and inpatient settings, the focus of research questions is slowly starting to shift toward the long-term consequences of infection with severe acute respiratory syndrome coronavirus (SARS-CoV-2). On February 11, 2020, the World Health Organization officially changed the name of the disease caused by SARS-CoV-2 to (COVID-19). With most of the re-

search focus of the biomedical scientific community on researching the epidemiology, etiology, diagnosis and treatment of COVID-19, the actual global pandemic, much new information about the disease is now being obtained on a daily basis.

While it has been both hypothesized and proven that COVID-19, a virus with a strong tropism for ACE2 receptors, which are present in most of the organ systems of the human body, causes lasting changes on both a molecular and macroscopic level, the exact epidemiologic dynamics and clinical manifestations of post-COVID have not been sufficiently researched. Of all the post-COVID manifestations and symptoms described in the literature, arterial hypertension seems to have gotten the short end of the stick. Despite being a risk factor for nearly every adverse cardiovascular

Corresponding author: *Assistant professor Ingrid Prkacin, MD, PhD*, University Hospital Merkur, Medical School, University of Zagreb, Croatia, Zajčeva 19
E-mail: ingrid.prkacin@gmail.com

event, renal disease and end organ damage known, the threat and significance of arterial hypertension are often underestimated by clinicians. This pattern of over-seeing one of the deadliest silent killers of today is unfortunately also noticeable in post-COVID research. While it has been established that COVID-19 can both cause “de novo” onset hypertension and worsen existing ones by interacting with both the RAAS¹ and endothelin² systems, a review of the literature describing the clinical aspects of the phenomenon produced sparse results, with the authors finding only a single survey³, a retrospective review⁴, and a case study⁵ regarding hypertension related to COVID-19. The aim of this paper, therefore, is to provide a window into this under-researched topic by describing a patient population suffering from post-COVID hypertension seen and treated by the authors, describing both their general attributes (age or gender) and specific clinical entities (arterial blood pressure, laboratory values, antihypertensive therapy, and other clinical conditions with which they are affected).

Methods

In this retrospective study, which lasted from January 2021 to January 2022, 199 patients (92 males, 107 females, with a mean patient age of 57.3 years) who have had COVID-19 were analyzed at the Emergency Department and Hypertension Clinic in Clinical Hospital Merkur, a tertiary care center in Zagreb, Croatia.

According to the accepted definitions of COVID-19 and its manifestations in regard to the time from a positive reverse-transcription polymerase chain reaction (PCR) test, the patients were divided into two groups: acute COVID patients (PCR test positive <30 days ago) and post-acute COVID patients (PCR test positive >30 days ago). Additionally, the post-acute group was subdivided into the following groups: sub-acute (30-90 days from a positive PCR test), chronic (90-180 days from a positive PCR test) and “long COVID” (>180 days from a positive PCR test to symptom onset).⁶

The patients’ laboratory test values, blood pressure, previous medical history, current therapy and history of COVID-19 were recorded and entered into a database. The inclusion criteria was a positive PCR test for COVID-19 at a single point in time, with a medical report

of the test result required as proof. The authors excluded patients with an incomplete medical history, an inaccurate timeline of the course of their COVID-19 disease course progression and consequences, and patients with symptoms of a respiratory infection or other infection without a report of a positive PCR test.

The data was statistically analyzed in JASP, an open-source statistics software package using distributive statistics and independent variable t-tests, to determine the similarities and differences between patients presenting with arterial hypertension and those presenting with other manifestations of post-COVID.

Results

A total of 199 patients with symptoms and manifestations related to COVID-19, with proof of a positive COVID-19 or SARS-CoV-2 PCR test, were analyzed. Among these patients, 32 of them (16.08%) had either new onset arterial hypertension (15 patients) or a worsening of an existing hypertensive condition (17 patients) related to COVID-19. In the hypertensive group, there were 18 (56.25%) female and 14 (43.75%) male patients with a mean age is 51 years. Regarding the time of symptom onset, the patients were divided into two groups: acute (4 patients, 2%) and post-acute COVID patients : sub-acute (11, 5.52%), chronic (8, 4%) and “long COVID” (9 patients, 4.52%). When comparing the hypertensive and non-hypertensive pa-

Table 1. Demographic data, median time from COVID diagnosis to symptom onset and blood pressure of patients from patient pool

	Male (n=92)	Female (n=107)	Mean
Age (years, median)	59	56	57.3
Number of hypertensive patients	14	18	16%
SBP (mmHg)	130	133	131.5
DBP (mmHg)	80	85	82.5
T2DM	10	12	11%
Time from positive PCR (months)	2	2	2

number (percentage).

SBP = systolic blood pressure; DBP = diastolic blood pressure; T2DM = type 2 diabetic patients, PCR = real-time reverse-transcription polymerase chain reaction, positive value determined at the beginning of the study from a single sample.

Table 2. Statistically significant different variables between the hypertensive and non-hypertensive patient group

	Hypertensive (n=32, 56.2 % F)	Non-hypertensive (n=167)	p value
Age (year)*	51.54±4.58	59.64±8.01	0.032
Time from positive PCR (months)*	3	1	0.014
SBP (mmHg)*	141.75±21.16	130.14±20.01	<0.001
DBP (mmHg)*	93.39±11.35	80.07±12.51	<0.001
Erythrocyte**	4.98	4.66	0.026
Hematocrit**	0.432	0.400	0.015

* mean ± SD ** number (percentage)

SBP = systolic blood pressure; DBP = diastolic blood pressure; PCR =real-time reverse-transcription polymerase chain reaction, time from positive test to symptom onset, value determined at the beginning of the study from a single sample. Erythrocyte = count (* $10^{12}/L$). Hematocrit (L/L).

tient groups, statistically significant differences were found for systolic blood pressure (median 141 mmHg HTN group vs 130 mmHg non-HTN group, $p < 0.001$) and diastolic blood pressure (median 93 mmHg HTN group vs 80 mmHg non-HTN group, $p < 0.001$), for age (median 51 years for hypertensive (HTN) vs 59 years for non-hypertensive (non-HTN), $p = 0.032$), erythrocyte count ($4.98 \cdot 10^9$ cells in HTN group vs $4.66 \cdot 10^9$ cells in non-HTN group, $p = 0.026$), and hematocrit (0.432 L/L in HTN group vs 0.40 L/L in non-HTN group, $p = 0.015$). There were no significant differences between the groups in other laboratory parameters, diabetes (only type 2) or other medical history and body mass index (BMI). In patients with existing hypertension (17 patients) 82% (15/17) had antihypertensive therapy in combination with angiotensin-converting enzyme inhibitors (ACEI) and calcium channel blockers or ACEI/diuretic. Only 12% patients (2/17) had monotherapy with ACEI.

Time from a positive PCR test to symptom onset was a median 3 months in HTN group vs 1 month in non-HTN group.

Discussion

We are well acquainted with the fact that hypertension is a “silent killer,” meaning that its consequences and severity are only felt in its late stages when end-organ damage has already ended, settled and become irreversible. We find it important to stress once again the necessity of follow-up exams for all patients following COVID-19.^{7,8} Considering the high infectiv-

ity rate of the virus and the number of people testing positive on both rapid antigen (RATs) and PCR tests daily, the question of the need for a post-COVID follow-up arises. The papers found during the authors' literature search on the topic of post-COVID hypertension estimated the incidence of arterial hypertension following COVID-19 to be between 9 and 12%^{5,9}. Our results suggest that, in a sample of 200 patients, the incidence is about 16%, and it is a relatively common occurrence. More effort should be directed to evaluating patients' blood pressure values following COVID-19 to make a timely diagnosis and start proper treatment as early as possible.

To generalize the results in this paper for the general population, approximately 1 in every 7 people infected by Covid-19 is at risk of developing either new onset hypertension or having an exacerbation and worsening of an existing hypertensive condition. Even if we consider that one of the departments included in this study is a hypertension clinic (even though less than one-fourth of our patient data came from that clinic), which we expected to skew mildly the results in favor of a larger incidence of hypertension, there is a real possibility that more than 10% of the general population is going to be affected by post-COVID hypertension, many of them undetected, especially among patients with no prior conditions in their medical histories. Since the mean time from a positive PCR test to the onset of hypertension in our studied population was approximately four and a half months, and the mean time to the onset of all other manifestations is three months, we suggest that follow-up physical ex-

ams, preferably by the patient's primary care practitioner (PCP), including measuring blood pressure, blood glucose values and serum creatinine, be done 30, 90 and 180 days after a positive PCR test.

Giménez-Miranda, et al. propose to measure endothelial function 6–12 months after an acute Covid-19 infection in hypertensive patients, especially if they have other vascular disease.¹⁰ Pulse wave velocity is the measure of arterial stiffness, which is directly connected to cardiovascular risk and hypertension-mediated organ damage. In future research on the detection of endothelial dysfunction in Covid-19 patients, we recommend measure pulse wave velocity, which we carried in patients with a hypertensive crisis.¹¹

In conclusion, post-COVID arterial hypertension is a real and serious consequence of a COVID-19 infection, affecting 1 in every 6 patients in our studied population, most often among women. While we found no laboratory markers that we can confidently use to predict arterial hypertension following COVID-19, we hope that the time frames provided in this paper - especially that for a positive PCR test to the onset of post-COVID symptoms - can help to provide a framework for sensible and adequate follow-up patient examinations after acute COVID-19, in order to make a timely diagnosis of any post-COVID sequelae and begin treatment before they develop into more serious conditions and syndemic problems.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

The authors state that this manuscript has not been published previously and is not currently being assessed for publication by any journal other than the *Acta Clinica Croatica*. The authors disclose that they did not receive any financial support for the study. No proprietary interest was involved in the study.

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Sažetak

ARTERIJSKA HIPERTENZIJA VEZANA UZ COVID-19 INFEKCIJU;
RETROSPEKTIVNA STUDIJA U SREDNJE EUROPSKOM TERCIJARNOM CENTRU*Đ. Delalić, J. Jug i I. Prkačin*

Pojavnost novoverificirane hipertenzije ili pogoršanje postojeće u pacijenata koji su preboljeli Covid-19 cilj je ove studije. Kako bi potvrdili da je pacijent bio kategoriziran kao Covid pacijent, morao je imati pozitivan PCR test.

Pacijenti su podijeljeni u grupe akutni i postakutni Covid. Analizirani su podaci vezani uz dob, indeks tjelesne mase, laboratorijske parametre, raniju medicinsku dokumentaciju te postojeću antihipertenzivnu terapiju.

U periodu od godinu dana obrađeno je 199 pacijenta koji su imali sve uključne kriterije. Od njih je u 32 (16%) utvrđena hipertenzija: u 15 s novoverificiranom hipertenzijom a u 17 pacijenata s pogoršanjem postojeće hipertenzije. Pojavnost hipertenzije bila je prema medijanu 3 mjeseca nakon potvrđene Covid-19 infekcije. Kada smo podijelili pacijente prema grupama: 4 pacijenta je bilo unutar akutnog perioda, 11 u subakutnom, 8 u kroničnom, a 9 pacijenata s hipertenzijom je bilo u grupi dugog (long) COVID-a. Populacija s hipertenzijom u odnosu na one koji nisu imali hipertenziju, imala je značajno viši sistolički (median 141 mmHg prema 130 mmHg, $p < 0.001$) i dijastolički (median 93 mmHg prema 80 mmHg, $p < 0.001$) krvni tlak. Utvrđena je statistički značajna razlika i prema dobi između skupine hipertoničara i nehipertoničara (median 51, prema 59 godina, $p = 0.032$). Pojavnost hipertenzije nakon Covid-19 infekcije nije rijetka.

Ključne riječi: *arterijska hipertenzija, COVID-19 infekcija, post Covid*