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Research Article

Impact of Covid 19 Vaccination on Outcome of BP among Hospitalized Covid 19 Patients

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Abstract

Purpose: A serious problem frequently encountered in patients hospitalized for Corona virus-2 disease (COVID-19) is the management of blood pressure (BP) values. This study aims to analyze the evolution of BP values in hospitalized patients and to assess the impact of vaccination on their clinical outcome.

Patients and Methods: This retrospective study was conducted on 85 patients divided into 2 groups: group A-39 vaccinated subjects and group B – 46 unvaccinated ones, admitted in the Infectious Diseases Clinic 1 of the Victor Babes Hospital Timisoara during the 6th wave of the COVID-19 pandemic. At the admission none of the patients, even those already diagnosed with systemic hypertension (SHT), had BP values over 150/90 mmHg. The severity of COVID-19 was determined based on the thorax computed-tomography findings and spontaneous peripheral oxygen saturation

Results: During hospitalization, the BP values were lower in group A compared to group B, and although they had more comorbidities vaccinated patients had fewer complications. The multilinear regression model determined that in both groups, inflammatory markers had statistically significant influence on the systolic BP values at discharge.

Conclusion: The study suggests that vaccination may have a positive impact on BP values and on the clinical outcome of patients with COVID-19.

Keywords: COVID-19; vaccinated against SARS-CoV-2; unvaccinated against SARS-CoV-2; systemic hypertension.

Introduction

The coronavirus disease (COVID-19) was initially, considered a respiratory pathology, but further research demonstrated that, even in mild to moderate forms, it is in reality a multi-systemic disease, with impact on several metabolic processes, and which determines a multitude of cardiovascular alterations [1, 2] or may even aggravate the preexisting ones [1].

Systemic hypertension (SHT), is often encountered in patients with COVID-19. Studies have shown that hypertensive patients are at a higher risk of developing more severe illness and complications from COVID-19, including pneumonia and acute respiratory distress syndrome (ARDS) [3].

There are several mechanisms by which the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes Covid-19, may influence blood pressure (BP), the principal pathophysiological pathways being the following ones: 1. A direct effect on the vascular system, by fixing on the angiotensin-converting enzyme 2 (ACE2) receptors from the surface of the endothelial cells and thus, downregulating them, concomitantly with the activation of the innate and adaptive immunity; [4] 2.The SARS-CoV-2 infection may induce a systemic inflammatory response, as the body releases cytokines to fight the virus, which can affect the vascular system causing inflammation, vasoconstriction and leading to endothelial dysfunction and increase BP as well [5]. 3. The sympathetic nervous system (SNS), which controls the "fight or flight" response, is activated during a viral infection, determining increased heart rate and vasoconstriction resulting in an increase in BP [6]; 4. The viral infection might activate the renin-angiotensin-aldosterone system (RAAS) also leading to the increase of BP [7]. 5. People with Covid-19 may experience changes in lifestyle such as physical inactivity and unhealthy diet, both are known to cause an increase in BP [8]. It's important to note that the relationship between SARS-CoV-2 infection and BP is complex, and more research is needed to fully understand the mechanisms involved [9].

The infection with the SARS CoV-2 virus, may produce a wide spectrum of symptoms, including fluctuation of BP values. Some studies have reported elevation of BP in COVID-19 patients, while other subjects experienced low values, sometimes even hypotension [10].The underlying mechanisms for these changes are not yet fully under-stood. A condition called "hypertensive emergency" has been reported in some patients with COVID-19, characterized by a rapid and severe elevation in BP values. This can be a serious complication and may be associated with a higher risk of complications and death [11], while other subjects may present hypotension. This can also be a serious complication and may be associated with poor outcomes. It is important to note that these blood pressure changes are not unique to COVID-19 and can occur in other viral illnesses [12].

In Romania, from the beginning of the pandemic until now, 15.78% of the country's population has been infected with the SARS-CoV-2 virus with a mortality rate of 3.26%. During the 6th wave of COVID 19, which lasted from 01 June 2022 until 30 November 2022, approximately 400,000 subjects have been infected and 2,000 deaths (0.5%) were reported national wide [13]. Comparing to the other mutation of this virus, detected since 2019, when the COVID-19 pandemic started (Alpha, Beta, Gamma, Delta) the Omicron type (subvariant BA5) [14], most frequently encountered during the 6th wave of COVID-19 in Romania, seems less aggressive, determining less frequently severe pulmonary injury, but being in turn more contagious increasing thus the risk of reinfection, due to mutations in the Spike protein that can disturb the response of neutralizing antibodies [15].

Since December 2020, the population has had access to the vaccines against the coronavirus disease. The efficiency of the vaccine was proven and it was well tolerated, but a decrease in protection against the disease was observed 6 months after vaccination [16]. In Romania, 4 vaccines are available: Pfizer, AstraZeneca, Moderna and Johnson&Johnson [17-19]. The Pfizer-BioNTech COVID-19 vaccine is a messenger RNA (mRNA) vaccine that works by teaching the body's cells how to make a protein that triggers an immune response. The immune system recognizes the protein as foreign and produces antibodies and T-cells to protect against future infection with the virus that causes COVID-19 [20]. The AstraZeneca COVID-19 vaccine is a viral vector vaccine that uses a harmless virus (a chimpanzee adenovirus) to deliver a piece of genetic material from the SARS-CoV-2 virus into cells in the body. This genetic material instructs the cells to produce a harmless piece of the virus, called the spike protein, which triggers an immune response. The immune system then recognizes the spike protein as foreign and creates antibodies and immune cells to target it, which can protect against future infections with the real virus [21]. The Moderna vaccine is a messenger RNA (mRNA) vaccine, while the Johnson & Johnson vaccine is a viral vector vaccine [22]. In Romania, 42% of the country's population is vaccinated against the SARS COV 2 virus.[23] It is well known that SARS-CoV-2 vaccines can influence the immune system in several ways. Because some vaccines typically contain harmless parts of the virus, such as the spike protein, which triggers an immune response, they stimulate the immune system to recognize and mount a defense against a specific pathogen, in this case, the SARS-CoV-2 virus [20, 21]. Another immune modulated response is the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-alpha (TNF-alpha) [23]. These cytokines help recruit and activate immune cells, contributing to the inflammatory response [23, 24]. The effectiveness of COVID-19 vaccines against infection and symptomatic disease decreases in time, by approximately 20–30 percentage at 6 months after full vaccination, as it is described in the meta-analysis of Feikin and al,[6] although the efficacy against

severe disease remains high. On the other hand, the 'spike protein' of the SARS CoV-2 virus, whose synthesis is induced by vaccines, binds to ACE2 receptors, determining their migration towards the inside of the cell. This would result in a drop of ACE2 activity on cell surfaces and therefore, in a relative deficiency of angiotensin I [7] with a relative excess of angiotensin II, which could explain, at least in part, the elevation of BP [25].

Starting from the premises that in vaccinated people, even if they have exceeded 6 months since the last vaccination, the amplitude of pathophysiological mechanisms responsible for BP fluctuations should be lower, we aimed to evidence in this study the difference regarding BP responses and the factors that influence them during the hospitalization for COVID-19, in vaccinated subjects in comparison to un-vaccinated ones. A second aim was to follow-up these patients, a month after discharge to ascertain the evolution of BP values.

Material and Methods

Study Population

This is a retrospective study that includes 85 individuals selected from all patients admitted to the Infectious Diseases Clinic 1 of Victor Babes Hospital Timisoara from 01 June 2022 to 30 November 2022, during the 6th wave of the COVID-19 pandemic ac-cording to the following inclusion/exclusion criteria.

Inclusion criteria: 1. Patients hospitalized during the 6th wave of SARS CoV-2, from 01 June 2022 to 30 November 2022; 2. age of over 18 years and capacity to sign an inform consent form; 3. a positive result of real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swabs confirming the SARS-CoV-2 infection: 4. the presence of a thorax computer tomography (TCT) per-formed in the emergency service or at admission in the infectious disease hospital.

Exclusion criteria: 1. Patients vaccinated against COVID-19 within less than 6 months prior to the inclusion in the study; 2. Subjects with severe forms of COVID-19 requiring, at admission, mechanical ventilation and/or admission in the intensive care unit; 3. Patients with acute or decompensated cardiovascular conditions such as acute myocardial infarction, acute coronary syndrome, acute pulmonary edema, chronic heart failure New York Heart Association (NYHA) class III or IV, stroke; 4. Patients with acute medical pathologies like comas, septicemias caused by other pathologies than COVID-19, upper or lower digestive tract hemorrhages, acute pancreatitis, severe anemias, renal failure; 5. Subjects requiring emergency surgical interventions, those with oncologic diseases requiring palliatives therapies.

All patients signed at the admission in the hospital the standardized inform consent of the Ministry of Health from Romania permitting the use of their medical data for medical research purpose. After the selection of suitable patients, their personal data were anonymized, and we collected from the hospital's informatic data-base their clinical and laboratory records. More than half of these patients declared themselves as previously healthy while those with associated pathologies were stable at the moment of admission in the hospital. The main reason for hospitalization were the symptoms caused by COVID-19. Subjects suffering from other acute or chronic decompensated diseases requiring specialized treatment, were referred to the respective clinics and hospitalized there. Even if not all patients were treated with antihypertensive medication at the admission, at one point during hospitalization all patients had blood pressure values higher than 140/80 mmHg, but under 170/95 mmHg.

The laboratory parameters from the admission, in-hospital stay and discharge were extracted from the hospital's data base, and information related to clinical data and evolution during each day of hospitalization were extracted from the hospital's archive. All patients had a TCT performed at admission, to establish the extend of pulmonary injury and it should be mentioned that 34 patients (39.53%) had no lung damage at admission. An electrocardiogram (ECG) was carried out in all cases, but the echocardiographic examination was limited due to the increased risk of infection for the medical personnel. 2D-echocardiography and color Doppler was performed only in patients whose health status worsened during hospitalization, who needed to be transferred to the intensive care unit, and in whom life-threatening cardiovascular complications, such as pulmonary embolism were suspected. As a standard of care, all patients had their body temperature, peripheral blood oxygen saturation (POS), heart rate and BP monitored twice daily, in the morning between 08:30 and 09:00 A.M., and in the afternoon between 17:30 and 18:00. Referring to POS levels, 53 patients (62.35%) had values under 95% and required oxygen administration at admission, and other 2 patients (2.35%) had normal POS at admission, but required oxygen therapy during hospitalization starting from day 9, respectively at day 10. The classification of the se-verity of COVID-19 was realized based on the extent of the lung injury on TCT and the results of POS.

Statistical Analysis

Data analysis was performed using the Statistical Package for the Social Sciences v.26 (SPSS, Chicago, IL, USA). Continuous variables were presented as mean and standard deviation (SD) or median and interquartile range (IQR), and categorical variables were presented as frequency and percentages. The results of the normality test (Shapiro-Wilk) showed a non-Gaussian distribution, suggesting that we should continue the analysis by using nonparametric tests. The individual impact of several confounding factors on the variance of continuous variables was assessed by building multivariate regression models. The quality of the model was described by using the accuracy of prediction and R squared. The predictors, in the final regression equations, were accepted according to a repeated backward-stepwise algorithm

(inclusion criteria $p < 0.05$, exclusion criteria $p > 0.10$) in order to obtain the most appropriate theoretical model to fit the collected data. We considered a p value < 0.05 to indicate a statistically significant difference.

Results

During Hospitalization

Taking into account that we aimed to study the differences concerning BP values between vaccinated and unvaccinated patients, we divided our study group into 2 subgroups: group A - 39 subjects who were vaccinated for more than 6 months prior to the actual infection with the SARS-CoV-2 virus, and group B - 46 patients which, due to various reasons, have not been vaccinated at all (Table 1).

We first categorized our patients' blood pressure readings and related data based on their vaccination status: two doses or three doses. Using advanced statistical methodologies, we then identified any notable differences in hypertension rates or its severity between these two groups, but there was no statistical difference between patients who received two or three doses of vaccine.

Another salient feature of our study was the exclusion criterion related to the time lapse since the last vaccine dose. It is recognized that post-vaccination immune response can vary between individuals. Some may exhibit a heightened immune response immediately after vaccination, while others may display a stronger response as more time elapses. The six-month duration allowed us to study a more averaged-out response amongst our cohort.

Although there was no statistical significant difference between the two groups concerning age, with a median of 72 years, male gender prevailed (59 men and 26 women, <0.001), as well as urban provenience in both groups (<0.001), see table 1. As for the vaccine types in group A, 13 patients (33.33%) were fully vaccinated with 3 doses of Pfizer, 25 patients (64%) were vaccinated with 2 doses, and only one patient (2.56%) was vaccinated with Johnson and Johnson, table 1.

Referring to risk factors, smoking was significantly more frequent (p=0.001) in group B, being noted in 10 subjects (21.73%), while only in 4 cases (10.25%) in group A. Regarding obesity, in group A, 9 patients (23.07%) were obese, with BMI values >30 kg/m2, in comparison to 12 patients (26.08%) from group B (p<0.001), as for overweight subjects, there was no statistically significant difference between the 2 groups. In group A, 10 subjects (25.64%) had normal weight, and BMI values <18.5 kg/m2 were found in only one patient (2.56%), while in group B 13 subjects (28.26%) had BMI values be-tween 18.6 and 24.9 kg/m2 (p<0.001), and 2 patients (4.34%) had BMI values <18.5 kg/m2, see table 1.

Table 1: Demographic parameters, risk factors and comorbidities of the study group.

Parameters	**Group A: 39 P**	**Group B: 46 P**	**p - value**
Age	72 ±16.42	72±14,14	0.566
Gender: Men Women	 23 (58.97%) 16 (41.02%)	 36 (78.26%) 10 (21.73%)	<0.001
Provenance: Rural Urban	 13 (33.33%) 26 (66.66%)	 26 (56.52%) 20 (43.47%)	<0.001
Vaccine type: Pfizer Johnson and Johnson	 38 (97.43%) 1 (2.56%)	 - -	 - -
Comorbidities and Risk Factors			
Smoking	4 (10.91%)	10 (21.73%)	0.001

Obesity Overweight Normal (BMI)	9 (21.73%) 19 (48.71%) 11 (28.2%) 26.6 [24.4 - 29.7]	12 (26.08%) 19 (41.3%) 15 (32.6%) 26.5 [24.6 - 29.73]	<0.001
Diabetes mellitus type 2	16 (41.02%)	9 (19.56%)	<0.001
Old myocardial infarction	2 (5.12%)	9 (19.56%)	<0.001
Stable angina pectoris	6 (15.38%)	7 (15.21%)	<0.001
Systemic hypertension	24 (61,53%)	37 (80.43%)	0.001
Stroke history	7 (17.94%)	8 (17.39%)	<0.001
Peripheral arterial disease	0	1 (2.17%)	<0.001
Atrial fibrillation	7 (17.94%)	9 (19.56%)	0.001

Notes: BMI - body mass index, p – statistical significance.

In group A, out of 39 subjects, 22 (56.41%) had cardiovascular comorbidities. Stable angina pectoralis was present in 6 subjects (15.38%), stroke and atrial fibrillation were present each in 7 subjects (17.94%) and silent myocardial ischemia in 2 subjects (5.12%) who had ST segment depressions on the EKG, but without retrosternal pain. 16 (41.02%) of the subjects had diabetes mellitus type 2, table 1.

Regarding the healthy patients, with no cardiovascular comorbidity or systemic hypertension, in group A, there were 11 patients (30.55%) aged 50.82±18.88 years, and in group B, there were only 6 patients (13.04%), aged 52 ±17.911 years (p-value < 0.001).

In group B, a total of 34 subjects (73.91%) had cardiovascular comorbidities, silent myocardial ischemia was detected in 9 subjects (19.56%), with ischemic modification present on the rest EKG. Regarding stable angina pectoris it was present in 7 (15.21%) patients and stroke in 8 (17.39%), while atrial fibrillation was more often encountered in group B – 9 cases (19.56%). In this group, peripheral arterial disease was found in one patient (2.17%). Diabetes mellitus was also an important comorbidity and all patients were treated with insulin due to a better control of blood sugar therapy during hospitalization, table 1.

Table 2: Details related to hospitalization and therapy.

Parameters	Group A: 39 P	Group B: 46 P	p - value
Days from symptoms onset to hospitalization	2.74±1.499	2.98±2.271	<0.001
Number of symptoms at admission	3.69±1.149	3.91±1.291	0.242
Number of symptoms at discharge	1.20±0.406	1.57±0.815	0.284
Days of hospitalization	10.03±6.730	10.91±6.865	0.153
POS at admission: Mild Moderate Severe	 13 (33.33%) 20 (51.28%) 6 (15.38%)	 17 (36.95%) 18 (39.13%) 11 (23.91%)	<0.001
POS saturation	92.13 [91-95]	91.72 [89.75-95]	0.628
Days of O_2 administration	4.26±5.134	5.63±7.132	0.307
Treatment for COVID-19			
Antiviral treatment	39 (100%)	44 (95.65%)	0.001
Corticotherapy	26 (66.66%)	35 (76.08%)	0.003

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Number of symptoms at discharge	1.20±0.406	1.57±0.815	0.284
Days of hospitalization	10.03±6.730	10.91±6.865	0.153
Anticoagulant therapy: Prophylactic dose	25 (64.10%) 0.4 ML – 11 0.6 ML- 13 0.8 ML -1	30 (65.21%) 0.4 ML -14 0.6ML – 15 0.8 ML - 1	<0.001
ICU stay	3 (7.69%)	5 (10.86%)	<0.001

Notes: POS–peripheral oxygen saturation; O2-oxygen saturation, ICU-intensive care unit.

The number of days elapsed since the apparition of the first symptom of SARS CoV-2 until the admission in the hospital was lower in group A compared to group B (p <0.001). The number of symptoms at admission and discharge as well, was some-what lower in group A, thus not statistically significant. In group A, the onset of symptoms started with 2.74 days before hospitalization, and a median of 3.69 symptoms was reported at admission. In group B, the onset of symptoms preceded with approximately 2.98 days the hospitalization, and at admission they had a median of 3.91 symptoms. Although, in group A, due to the persistence of symptoms, the median du-ration of hospitalization was 10 days, versus 10.91 in group B, the hospitalization du-ration was shorter in group A compared to non-vaccinated patients, but not statistically significant (p=0.153), see table 2.

In the context of SARS Cov-2 infection, the classification of the disease is determined based on POS saturation levels. According to the internal protocol of SARS-CoV-2 infection, at Victor Babes Timisoara Hospital, the disease is classified into mild, moderate, and severe forms. This classification system allows healthcare professionals to assess the severity of the infection and provide appropriate medical interventions. 30 patients (35.29%) having mild form with POS between 95 and 100%, 38 of them had moderate form with POS between 94-91% (44.70%), and with severe forms, with POS under 90% - 17 patients (20%).

During hospitalization, 26 patients (66.66%) required O2 administration, by facial mask, the average duration of oxygenotherapy being 4.26 days in group A, in comparison to group B, where 29 subjects (63.04%) needed O2 administration, the average duration of this therapy being 5.63 days (p=0.307), see table 2.

All patients from group A and B received antiretrovirals: in group A 24 subjects (61.53%) had Remdesivir 100 mg/day in their treatment and 15 (38.46%) had Favipiravir 600 mg/day for 10 days. In group B, 23 subjects (50%) had Remdesivir 100 mg/day for 5 days and 23 (50%) Favipiravir 600 mg/day for 7.61±2.42 days. Regarding corticotherapy 26 subjects (66.66%) from group A and 35 (76.08%) from group B received corticosteroids (p-value = 0.102), all had 16 mg/day for the first 5 days, then 8 mg/days for the last 5 days. Clexane and Fraxiparine were used as anticoagulants in prophylactic dose. In group A, 11 patients (28.20%) received 0.4 ml, 13 (33.33%) 0.6 ml, and 1 (2.56%) had 0.8 ml. In group B, 14 subjects (30.43%) had 0.4 ml, 15 (32.60%) had 0.6 ml and 1 (2.17%) had 0.8 ml.

A special attention was granted to the patients with systemic hypertension and under previous treatment with BP lowering drugs, but also to those discovered with elevated BP values at the first evaluation. In group A, there were 24 patients (61.3%) with systemic hypertension; of them, 6 subjects (15.38%) had isolated systolic BP (SBP) values ≥140mmHg at admission and from this subgroup, 5 (12.8%) individuals continued to present elevated BP at discharge. Diastolic BP (DBP) was over 90 mmHg in 6 patients (15.38%) at admission, and remained elevated in 3 subjects (7.69%) at dis-charge. 15 patients (38.46%) were not diagnosed with systolic hypertension, but at ad-mission they had SBP values ≥140mmHg. It should be mentioned that they had elevated values only on admission, these values normalizing from the second day of hospitalization. Only one person had values of over 140 mmHg also at discharge, requiring the initiation of one or two new anti-hypertensive drugs.

In Group B, 37 patients (80.43%) were diagnosed with systemic hypertension before admission. 13 of them (30%) had SBP ≥140mmHg at admission, and 7 at discharge (15.21%), while DBP was increased in 3 patients (6.52%) at admission, and in 4 (8.,7%) at discharge. Nine subjects (19.56%) were not treated with antihypertensive drugs and 6 of them (15.21%) had SBP values ≥140 mmHg at admission, one patient (2.17%) had elevated values

on day 2 of hospitalization, and another one (2.17%) on day 7 of hospitalization. At discharge, 2 of them had values over 140 mmHg at discharge (table 3).

In group A, out of the 39 patients, only 15 patients (38.46%) remained hospitalized after the 9th day of hospitalization, all hypertensive, over 60 years old. The maximum duration of hospitalization was 27 days, required in 3 cases.

In group B, out of the 46 patients, 18 (39.13%) remained hospitalized after the 9th day of hospitalization, all diagnosed with systemic hypertension degree II and III, 3 of them newly diagnosed, over 60 years old. The maximum duration of hospitalization in this group was 33 days, in one patient.

Regarding SBP in group A and in group B during hospitalization, we observed significant trends over a nine-day period. On the first day, the BP in Group A was recorded at 132 mmHg, slightly higher in Group B, at 134 mmHg. During follow-up, we noticed in the first 3 days a consistent decline in SBP in both groups, with the lowest values recorded in the third day of hospitalization, of 124 mmHg in group A, respectively 125 mmHg in group B. In the following 4 days, the SBP values stabilized at around 126 to 127 mmHg in group A and at slightly higher values in group B. Starting from the 8th day SBP values in both groups started to decline, reaching values of 121 mmHg in group A, respectively 122.5 mmHg in group B, at day 9. These findings indicate a consistent reduction in BP for both vaccinated and unvaccinated patients during their hospitalization. However, patients from group A had a slightly lower average SBP throughout the follow-up period compared to those from group B, see Figure 1. (p=0.230).

Figure 1: Average daily excursion of SBP during hospitalization in group A (vaccinated) versus group B (un-vaccinated).

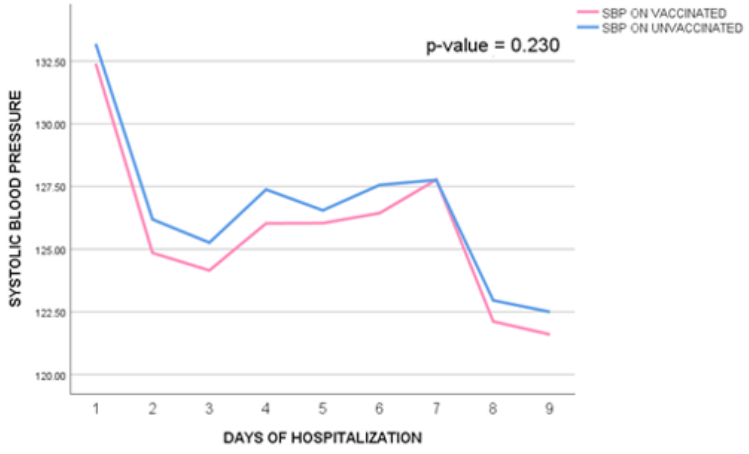

Table 3: Parameters regarding blood pressure in the two groups.

Parameters	Group A: 39 P	Group B: 46 P	p - value
Nr. of patients with SH	24 (61,53%)	37 (80.43%)	0.066
SBP at admission (mmHg)	126.05 [108 – 141]	137.27 [131 – 146]	0.711
DBP at admission (mmHg)	75.54 [65 – 89]	73.91 [67 – 80]	0.145
SBP at discharge (mmHg)	125.14[110.5 – 135.75]	128.56 [117.25 – 138]	0.357
DBP at discharge (mmHg)	71.36 [61.5 – 78]	72.50 [65.5 – 80.75]	0.010
SBP at 1 month	122.26 [122 – 130]	127.25 [120.25–132.25]	0.185
DBP at 1 month	58.95 [56.5– 61]	70.13 [60 – 75]	0.205
Number of antihypertensive drugs at admission	1.31 [0 – 2]	1.72 [0 – 3]	0.450
Number of antihypertensive drugs at discharge	1.51 [0 – 2]	1.84 [0 – 3]	0.369

Notes: SH-systemic hypertension, SBP-systolic blood pressure, DBP-diastolic blood pressure.

In group A, 6 patients (15.38%), with the mean age = 78.33 ± 9.97 years, 4 males and 2 women, one of them not being diagnosed previously with hypertension, continued to have elevated SBP at discharge requiring the initiation of one or two new antihypertensive drugs. These patients had a prolonged hospital stay, with a median duration of 17.16 days and presented at discharge, elevated levels of CRP – 21.01±11.59 mg/l, and ferritin – 851.06±481.05 ng/ml.

Regarding DBP, 3 patients (7.69%), 3 women, presented at discharge elevated values. All were overweight, had a mean age of 77±1 years and with a lung injury of 6.66±5.77% on CTC. These patients were treated with antihypertensive medication in monotherapy and in one patient another antihypertensive drug was added at dis-charge. This subjects continued to have elevated level of inflammatory markers at dis-charge: CRP 9.72±8.04 mg/l, and ferritin 315.963±183.974 ng/ml.

In group B, 7 men (15.21%) presented elevated SBP at discharge, with mean aged 67.71 ± 11.95 years, a median BMI of 27.02, with a lung injury of 11%, with a median duration of hospitalization of 9 days. Two (4.34%) of them were not diagnosed with hypertension before. At discharge, this patient presented the following mean biological parameters: leukocytes – 10.79±2.73 µL, CRP 5.72±2.95 mg/l, D-dimers – 0.72±0.32 µg/ml, procalcitonin – 0.48±0.85 mg/ml2, ferritin – 725.28±395.84 ng/ml.

Regarding DBP at discharge, in group B, 4 patients (8.69%) had elevated values, 3 men and 1 female, median aged 65.50 ± 14.17 years, with a median BMI of 25.45, pulmonary injury – 10%, duration of hospitalization - 8 days, onset of symptoms 1.62 days before hospitalization. Three subjects (6.52%) had 2 antihypertensive drug at hospitalization and at discharge, and 1 patient (2.17%) received no antihypertensive treatment before hospitalization. At discharge this patient presented the following mean biological parameters: D-dimers 0.71±0.244 µg/ml, CRP 4.24±4.67 mg/l, procalcitonin 0.94±1.01 mg/ml2, ferritin 482.775±454.641 ng/ml.

Discharge from Hospital

From the total number of 85 patients 15 died (17.64%) and 69 (82.35%) were dis-charged alive. Three patients from group A, died (2 men and one woman). It should be mentioned that only one person was infected with SARS CoV2 in the past, now being the second reinfection, but she was discharged. In group B - 10 unvaccinated people died, 2 women and 8 men, all requiring oxygen therapy since admission.

In group A were fewer complications diagnosed during hospitalization, as in group B. The complications that were monitored were oxygen therapy at home, anemia, sepsis, enterocolitis, fasting hyperglycemia. From group A, 5 patients (12.82%) required oxygen therapy at home, compared to group B, where only 2 patients (4.34%) required oxygen therapy at home (p-value < 0.001). During hospitalization, 2 patients from both groups, (5.12%, respectively4.34%), were diagnosed with enterocolitis with Clostridioides difficile and received antibiotic therapy. Another complication encountered was sepsis, present more frequently in the unvaccinated group (p-value < 0.001). Ten subjects (25.64%) from group A and 12 from group B (26.08%) had procalcitonin values > 0.5 ng/mL2 and received specific antibiotic therapy.

In most cases, during hospitalization, laboratory parameters were collected twice a week, and in 21 patients (53.84%) from group A and in 30 patients (65.21%) from group B, decreases in hemoglobin below < 12 g/dl were reported, anemia being the most frequent complication during hospitalization in both groups (p-value < 0.001).

Following the laboratory results, 10 patients from group B (21.73%) and 5 (12.81%) from group A had fasting blood glucose values > 100 mg/dl (p-value < 0.001).

The biological data at discharge improved in comparison to those from admission, most of the parameters returning to values within normal limits at the time of discharge. There was a significant difference regarding the erythrocyte sedimentation rate (ESR) values at discharge (p=0.08), and creatinine value at admission (p=0.097) between the two groups (Table 4).

Table 4: Biological parameters of Group A and B during hospitalization and at discharge.

	Hospitalization			Discharge		
	A	**B**	**p-value**	**A**	**B**	**p-value**
Leukocyte (µL)	10.47 [5.51 - 15]	8.72 [5.92 – 11.14]	0.238	10.21 [7.67 -11.41]	9.57 [7.23 – 11.10]	0.215
ESR (mm/h)	40.25 [10 - 60]	43.48 [20 - 65]	0.576	24.05 [5.5 – 23.75]	22.09 [5 - 20]	0.086
D-dimer (µg/mL)	2.07 [0.75 - 1.60]	2.59 [0.64 – 1.9]	0.230	166 [0.70 -2.14]	1.62 [0.59 - 2.20]	0.197
C Reactive Protein (CRP) (mg/l)	39.20 [12.55 - 79.87]	56.04 [23.36 - 109.60]	0.238	9.23 [1.37 – 14.95]	32.60 [6.73 – 79.62]	0.237
Interleukine-6 (pg/ml)	4.41 [1.5 - 17.24]	18.48 [7.53 - 33.96]	0.250	6.70 [1.50 – 8.40]	17.64 [2.60- 20.73]	0.425
Procalcitonin (ng/ml2)	1.81 [0.05 - 0.73]	0.65 [0.06 - 0.42]	0.394	0.19 [0.02 - 0.25]	0.13 [0.01 - 0.15]	0.393
Ferritin (ng/ml)	672.26 [264.64 – 871.54]	974.65 [381.47 – 1238.05]	0.238	406.01 [221.29 – 524.46]	584.52 [189.76 – 727.90]	0.237
ALT (U/L)	53.36 [16 – 46.20]	38.85 [18.45 - 46.40]	0.250	57.38 [16.40 – 44.82]	34.56 [14.25 – 43.20]	0.241
AST (U/L)	52.91 [21.10 – 59.50]	40.08 [23.05- 48.80]	0.193	42.60 [15.30 – 35.45]	32.08 [18. 75 – 39.35]	0.263
Urea (mg/dl)	48.62 [31.50 – 62.10]	59.89 [42.05 – 80.94]	0.244	52.98 [27.27 – 67.15]	55.01 [36.15 – 59.65	0.237
Creatinine (mg/dl)	1.02 [0.66 – 0.94]	1.10 [0.71 - 1.26]	0.097	0.98 [0.62 - 0.84]	0.84 [0.61 - 1.01]	0.250
GFR (ml/min/1.73m2)	95.41[71 - 117]	84.34[54.75 - 117]	0.329	107.30 [89 – 128.67]	105.94 [69.75 - 154]	0.273

Notes: ESR- Erythrocyte sedimentation.

The multilinear regression model determined that in group A, inflammatory markers had statistically significant influence over the SBP at discharge.

The coefficient for CRP at discharge (0.628) is significant at the 5% level, with a p-value of 0.010. As CRP increases by one unit, SBP at discharge should increase by 0.628 units. Also the coefficient for feritin at discharge (0.022) is significant with a p-value of 0.008, while feritin increases by one unit, SBP at discharge should increase by 0.022 units. The multiple regression R2 value = 0.575 shows us that the regression model explains 57.5% of the SBP variation at discharge. The adjusted R2 value of 0.469 takes into account no independent variables and adjusts the R2 value. The statistical F value of 5.415 and p-value= 0.001 tests the general significance of the regression mod-el. The p value shows that the model is significant, so taken together, the 7 variables (age, leucocytes at discharge, D-dimers at discharge, CRP at discharge, IL-6 at dis-charge, procalcitonin at discharge and feritin at discharge) have a significant influence on SBP at discharge on vaccinated patients (table 5).

Table 5: Linear regression of SBD in group A at discharge.

	B	Std. Error	Beta	T	p-value
CRP discharge	0.628	0.228	0.421	2.754	0.010
Feritin discharge	0.022	0.008	0.451	2.860	0.008

Notes: CRP- C Reactive Protein.

The multilinear regression model determined that in group B, inflammatory markers also had statistically significant influence over the SBP at discharge. The coefficient for feritin at discharge (0.014) is significant with a p-value of 0.030. While feritin increases by one unit, SBP at discharge should increase by 0.014 units. The multiple regression R2 value = 0.258 shows us that the regression model explains 25.8% of the SBP variation at discharge. The statistical F value of 2.432 and p-value= 0.071 tests the general significance of the regression model. The p value shows that the model is significant, so taken together, the 4 variables (CRP at discharge, IL-6 at discharge, procalcitonin at discharge and feritin at discharge) have a significant influence on SBP at discharge on unvaccinated patients (table 6).

Table 6 Linear regression of SBD in group B at discharge.

	B	**Std. Error**	**Beta**	**T**	**p-value**
Feritin discharge	0.014	0.006	0.480	2.282	0.030

A month after discharge

A month after discharge, in group A, all patients had BP values within normal limits. All patients followed the treatment prescribed at discharge from the infectious disease clinic and monitored their BP two times a week. The reported symptoms at discharge were fatigue (100%) and a productive cough (2.56%) in a man. One month after discharge, fatigue was observed, still present in all vaccinated patients.

In this group, six patients (15.38%) showed elevated SBP values at discharge. The addition of one or two antihypertensive drugs was required for these patients. These patients also had a longer median hospital stay of 17.16 days. Regarding DBP, three patients (7.69%) presented elevated DBP at discharge. These individuals required antihypertensive medication. In one case, an additional antihypertensive drug was added at discharge. Patients with elevated BP at discharge from Group A showed increased inflammatory markers, indicating a potential link between inflammation and hypertension.

Group A's SBP: Reduced from 126.05 at admission to 122.26, with an increase in antihypertensive drug usage from 1.31 to 1.72

In group B, 30 days after discharge, 3 males (6.52%) patients continued to have uncontrolled systemic hypertension.

In group B, seven males (15.21%) showed elevated SBP values at discharge. The mean age was slightly lower than Group A at 67.71 ± 11.95 years. Two of these patients were not previously diagnosed with hypertension. Regarding DBP, four patients (8.69%) had elevated values at discharge. Three were on two antihypertensive drugs during hospitalization, which continued upon discharge. One patient wasn't previously on any antihypertensive treatment.

Group B's SBP: Reduced from 137.27 at admission to 127.25 with an increase in antihypertensive drugs from 1.51 to 1.84.

It's essential to note that in both groups, while BP decreased, the number of antihypertensive drugs administered increased. This suggests that the reduction in BP wasn't purely due to the natural recovery from COVID-19 or the effects of the vaccine but also due to intensified medical management.

Discussion

The occurrence of BP fluctuations was frequently observed in patients infected with the SARS-CoV-2 virus since the early stages of the COVID-19 pandemic. It be-came also evident that individuals suffering from systemic hypertension develop more severe forms of disease and that they are more predisposed to develop cardiovascular complications or post-COVID syndromes. What remained totally unclear is why although most patients present elevated values of BP, some even develop hypotension during the disease.

As stated in the medical literature, the vaccines against COVID-19 may influence BP values for more than 6 months, this is why we selected only patients who have not been vaccinated against COVID-19 in the last 6 months.

There have been some reports of temporary fluctuations in BP following COVID-19 vaccination, but the evidence is still limited. One study published in the New England Journal of Medicine found that among a group of nearly 1,200 health care workers who received the Pfizer-BioNTech COVID-19 vaccine, 3% of recipients reported symptoms such as headache, fatigue, and dizziness that started within 15 minutes of receiving the vaccine and lasted for about a day. Some of these symptoms can be associated with changes in BP [26].

Another study evidenced that out of 45,000 people who received the Moderna COVID-19 vaccine, 4% of vaccine recipients had adverse events following vaccination, with hypotension (low BP) being the most commonly reported [27].

It is important to note that these BP changes are typically short-lived and do not cause any serious harm. It's also worth mentioning that there's no long-term studies or data available yet about the effect of COVID-19 vaccination on BP after a while [28].

A study of 357,387 subjects reported 13,444 events of elevated BP (3.20%). Of these, 0.6% were cases of stage III systemic hypertension and needed additional care. In conclusion, high BP is not uncommon after the COVID-19 vaccination, but its benefits far outweigh possible risks [29].

Hypertension is a major risk factor when it comes to SARS-CoV-2 infection. In a recent study [29], hypertension was associated with a 2.5-fold increased risk of both increased disease severity and mortality in COVID-19 patients. This heightened risk for hospitalization with COVID-19 is especially concerning given that nearly half of all adults are hypertensive [30]. The researchers also discovered that chronic kidney disease, having had a heart attack, or heart failure greatly increases the risk of hospitalization after infection. When the team excluded patients who were diagnosed with these conditions, the risk for hospitalization was still substantial for those with hypertension alone. The study also found that the risk of hospitalization increased with age and time elapsed between vaccination and infection, thus this research emphasizes the importance of regular medical care for those with hypertension and other chronic conditions [31].

Based on available data, there have been reports of increased BP after COVID-19 vaccination. A meta-analysis of six studies showed that the proportion of patients with abnormal or increased BP after vaccination was estimated to be 3.20% (95% CI: 1.62-6.21) [25, 32]. However, there is no immunologic explanation for vaccinations, including mRNA vaccines, to cause persistent elevation of BP [33].

It is unclear if this effect persists beyond the short-term and further research is needed to fully understand the mechanisms behind this phenomenon. As for the specific timeframe of one month after vaccination, there is insufficient information to provide a definitive answer at this time.

Study limitations: the main limitation of this study is the reduced number of patients, but it was difficult to find suitable patients who had stable associated medical conditions at the moment of the admission and who were vaccinated for more than 6 months. Another reason for our small study group was due to the fact that hospitalization was no more mandatory for COVID 19 patients and the majority of subjects refused to be hospitalized, except for those with severe symptoms. It should also be considered that the infection with the Omicron variant did not result so often in moderate and severe forms.

Conclusion

Patients with systemic hypertension and COVID 19 who were vaccinated against the SARS COV 2 infection, had fewer complications at discharge and blood pressure values within normal limits 30 days after discharge, compared to those who were not vaccinated. In our study, we observed that markers of inflammation, such as the values of ferritin, may influence the systolic blood pressure response during hospitalization in patients with COVID-19, but further research is needed.

Disclosure

Author Contributions: Conceptualization, D-M. M., D-M. G., G-E. F., N-I. V., C. T. and A. E.; methodology, D-M. M., C.T. and D-M. G. software, D-M.M; validation, D-M. M., D-M. G., G-E. F., N-I. V., C. T. and A. E.; formal analysis, D-M. M., C. T and D-M. G.; investigation, D-M. M., C.T. and D-M. G...; resources, D-M.M .; data curation, D-M.M., C.T and D-M.G.; writing—original draft preparation, D-M. M., D-M. G., G-E. F., N-I. V., C. T., A. E.; writing—review and editing, D-M. M., C. T and D-M. G.; visualization D-M. M., D-M. G., G-E. F., N-I. V., C. T., A. E.; supervision, , D-M. M. and C. T.; project administration, D-M. M., C.T and D-M. G.; funding acquisition, not applicable. All authors have read and agreed to the published version of the manuscript.

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