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Application of 24-Hour Ambulatory Blood Pressure Monitoring to Measure the Effect of COVID-19 Infection on Cardiovascular Health: A Pilot Study

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Abstract

Background: Up to 30% of patients hospitalized with Coronavirus Disease 2019 (COVID-19) have cardiovascular complications. Identifying early vascular changes that precede overt development of cardiovascular disease (CVD) is crucial for preventing and treating CVD. Therefore, we examined 24-hour ambulatory blood pressure (ABP) parameters that could serve as early markers of vascular change in COVID-19 survivors.
Methods: We recruited three categories of adults (18-65 years of age) who had either: (1) COVID-19 with hospitalization; (2) COVID-19 with no hospitalization, or (3) no history of COVID-19. Using a validated oscillometric ABP monitor (Mobil-O-Graph), we measured 24-hour ABP profiles including peripheral and central BP, augmentation index (AIx@75), and pulse wave velocity (PWV). We performed an analysis of variance and chi-square tests to compare means and standard errors of continuous and categorical variables, and created linear models to examine group difference in mean 24-hour ABP profiles across the three study groups, controlling for confounding factors.
Results: Thirty-three participants completed the study. On average, participants who had been hospitalized due to COVID-19 were older compared with those with COVID-19 but not hospitalized and those who did not contract COVID-19. After adjusting for potential confounders, participants with COVID-19 who were hospitalized had higher AIx@75.
Conclusion: Our finding suggests that 24-hour ABP monitoring profiles, especially AIx@75, may provide early information regarding cardiovascular complications in patients hospitalized with COVID-19. A large-scale study is warranted to confirm the findings of our study.
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Keywords: 24-hour ambulatory blood pressure; Blood pressure variability; COVID-19; Diastolic; Night dipping; Systolic

Plain Language Summary

- The study provided preliminary evidence for the potential role of augmentation index obtained from a non-invasive 24-hour ambulatory blood pressure device in identifying early vascular changes following COVID-19 infection related hospitalization.
- Patient with COVID-19-related hospitalization demonstrated different pattern of 24-hour ambulatory blood pressure than COVID-19 patients with no hospitalization and those with no COVID-19 infection.

Introduction

Throughout the Coronavirus Disease 2019 (COVID-19) pandemic, our understanding of the SARS-CoV-2 virus long-term effects has progressively expanded. Although the virus affects multiple organ systems in the post-acute phase, it's most notable effects are on the cardiovascular system, manifesting as an increased risk for arrhythmias, myocarditis, cardiac injury, heart failure, and hypertension [1-4]. Evidence shows that SARS-CoV-2 increases the risk of cardiovascular disease (CVD) by infecting artery wall tissue leading to endothelial dysfunction, inflammation, thrombosis, and microvascular obstruction [5]. Given the notable cardiovascular effects of COVID-19, the need for continuous cardiovascular monitoring techniques becomes increasingly evident. Twenty-four-hour ambulatory blood pressure (ABP) monitoring is an advanced method that continuously records several blood pressure (BP) parameters such day/night systolic BP (SBP) and diastolic BP (DBP), night-time dipping, morning surge, pulse wave velocity (PWV), and augmentation index at heart rate of 75 per minutes (AIx@75) over a 24-hour cycle. This technique is particularly crucial in the context of COVID-19, as it helps in the early detection and management of potential cardiovascular complications that are now known to be associated with COVID-19. Unlike standard clinic-based BP measurements, which only offer a snapshot in time, 24-hour ABP monitoring delivers a comprehensive profile of BP changes that are strongly predictive of incident CVD, future cardiovascular events, and mortality [6,7].

Previous studies examining the associations of COVID-19 infection with 24-hour ABP have shown mixed results. Two studies [8,9] showed no significant increases in 24-hour ABP parameters 4-8 months after COVID-19 infection. However, other research [10,11] focusing on patients with history of COVID-19-related hospitalization reported elevated 24-hour ABP and office BP [12] readings 6 months after discharge. Additionally, a study [4] using clinic BP measures also reported that COVID-19 patients had elevated SBP and DBP after 31.6 ± 5.0 days on average after diagnosis. The variance in existing findings can likely be ascribed to a range of factors, including the diverse severity of COVID-19 symptoms experienced by individuals and the critical aspect of when the outcomes are measured after COVID-19 infection. For example, one [8] of the two studies that reported comparable 24-hour ABP among groups reported a significant inverse relationship between time since COVID-19 diagnosis and BP, with higher BP readings when measured closer to the acute infection. Recognizing the significance of contextualizing the severity of COVID-19 infection, in the current study, we recruited three groups of participants (COVID-19 with hospitalization, COVID-19 with no hospitalization, and no COVID-19). We also incorporated a comprehensive analysis of self-reported symptoms associated with COVID-19, providing a more granular view of the disease's impact. Additionally, we integrated the fatigue severity score scale, recognizing that fatigue can be a pervasive and often underestimated aspect of the post-COVID-19 experience. The aim of this pilot study was to generate preliminary data on the association between COVID-19 severity and 24-hour ABP parameters after ≥ 3-months of initial diagnosis of COVID-19.

Methods

Study Design, Setting, and Participants

In this prospective cross-sectional study, we recruited adults (18-65 years of age) who met one of the following three criteria: had a diagnosis of COVID-19 (≥3 months ago) that resulted in hospitalization; had a diagnosis of COVID-19 (≥3 months ago) that did not result in hospitalization; or had a negative COVID-19 test ≥3 months ago and did not have history of COVID-19 diagnosis. Exclusion criteria included: (1) receiving treatment for high BP, (2) a diagnosis of atrial fibrillation or other arrhythmia, arteriovenous fistula in the brachial arm, or lymphedema, (3) those with history of angina pectoris, myocardial infarction, stroke, heart failure, peripartum cardiomyopathy, or bleeding disorder, (4) those who were currently on blood thinners, or (5) body mass index≥ 40 kg/m^2.

Procedures

After obtaining written consent, participants visited our research clinic. During this baseline visit, participants completed: 1) a baseline questionnaire including demographic characteristics and fatigue using the fatigue severity score [13]; 2) anthropometric measurements (weight, height, and upper-mid-arm circumference); and 3) brachial artery resting BP measurement using Omron oscillometer device (Omron 907L, Omron, Lake Forest, IL) [14] per the American Heart Association and the international consensus on standardized clinic BP measurement guidelines [15,16]. We obtained three BP readings, and the mean of the three measurements was used for analysis. When leaving the clinic, participants were fit with the ABP monitor (Mobil-O-Graph, IEM GmbH, Stolberg, Germany), which they wore for 24 hours.

24-Hour ABP Monitoring

The 24-hour ABP monitoring device was configured to record BP measurements every 30 minutes during the day (while awake) and every hour during the nighttime (while asleep) based on the participants-reported wake and sleep times. In accordance with the American Heart Association guidelines for BP measurement, appropriately sized cuffs were applied to the participants' non-dominant mid-upper arm circumferences [16]. Participants were instructed to maintain their usual daily activities during the measurement period, ensuring their arm remained still and extended at cuff inflation. Subsequently, all ABP parameters, including 24-hour ambulatory brachial and aortic BP (cSBP, cDBP), mean arterial pressure, (AIx@75), PWV, and related metrics, were extracted from the device using HMS Client Server software. Utilizing these data, we computed the average values for 24-hour ABP parameters. Nocturnal BP dipping was assessed by calculating the percentage of BP drop, employing the formula: dipping (%) = (mean daytime BP-mean nighttime BP) * 100/ mean daytime BP.

This percentage was categorized into two groups: non-dipping BP (defined as a < 10% decrease) and dipping (10% to 20% decrease) [17]. In addition, we calculated ABP variability indices including standard deviation (SD), coefficient of variation (CoV), weighted standard deviation (wSD), [18] average real variability (ARV), [19,20] and successive variation (SV) [21].

Data Analysis

Descriptive statistics were used to describe the sample characteristics by COVID-19 diagnosis and hospitalization status. Adherence/compliance to 24-hour ABP monitoring was assessed by calculating the percentage of participants completing the measurement over 24 hours and the number of valid BP readings obtained over the period. Participants who had at least 70% of the expected number of valid BP readings within the 24-hour period were considered compliant and included in the analysis [22,18]. Analysis of variance and chi-square tests were used to compare means and standard errors of continuous and categorical variables across the three study groups. Multivariable linear regression was conducted to examine group difference in mean 24-hour ABP profiles across the three study groups. The multivariate linear regression model was adjusted for timing of BP, age, sex, race, smoking, weight, presence of chronic illness, and standard errors for clustering by subject. The additional adjustment for standard errors for clustering was necessary because the repeated measures within a subject were likely correlated, not independent. The data underlying this article cannot be shared publicly due to the small sample size and the risk this might cause for the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

Results

Thirty-eight participants successfully completed the study procedure. Of those, four participants were excluded because less than 70% of the desired ABP readings were obtained during the 24-hour cycle. On average, participants with COVID-19 diagnosis that resulted in hospitalization were older (mean age=56 years, SD=6) than those with the diagnosis of COVID-19 who were not hospitalized (mean age=38 years, SD=14) and those with no-COVID-19 diagnosis (mean age=35 years, SD=12). Patients with COVID-19 hospitalization had higher mean fatigue severity score (38.8) than those with COVID-19 who were not hospitalized (32.4) and those with no COVID-19 (29.5). A fatigue severity score of 36 or more suggests that an individual is suffering from possible fatigue and require further investigation. Table 1 provides a summary of selected demographics, anthropometric measurements, BP, and fatigue score by COVID-19 diagnosis and hospitalization status. Compared to COVID-19 patients that were not hospitalized, those with COVID-19 related hospitalization were more likely to report cough, fatigue, fever, hoarse voice, shortness of breath, and weakness (Figure 1). Fifty percent of COVID-19 patients requiring hospitalization experienced an illness duration exceeding 4 weeks. Among COVID-19 patients admitted to the hospital, 25% had an illness duration ranging from 3 to 4 weeks, while another 25% had an illness duration of 1 to 2 weeks. Conversely, 37.5% of those not requiring hospitalization experienced an illness duration exceeding 4 weeks, and 62.6% of COVID-19 patients without hospitalization had an illness duration of less than two weeks. Compared to those not hospitalized with COVID-19 and those with no COVID-19 diagnosis, 24-hour SBP, DBP, cSBP, cDBP, AIx@75, PWV, SD, COV, wSD, ARV, and SV parameters were mostly higher for patients hospitalized with COVID-19 (See Figures 2a-f). However, these differences were not statistically significant. After adjusting for timing of BP (day vs. night), age, sex, race, smoking, weight, presence of chronic illness, and standard errors (to account for potential within subject correlation in repeated BP measures), patients with COVID-19 that did not result in hospitalization had lower AIx@75 (mean difference of 4.30, SD = 2.38; $p < 0.1$) than those hospitalized with COVID-19 (Table 2). Other 24-hour ABP parameters (SBP, DBP, cSBP, cDBP, and PWV) were also lower for COVID-19 patients that were not hospitalized when compared to those who were hospitalized, although the difference did not reach statistical significance in the adjusted model.

Blood pressure parameters and indices	Total	COVID-19 with hospitalization (n=4)	COVID-19 without hospitalization (n=17)	No COVID-19 (n=13)	p-value (Kruskal-Wallis Test/Chi-square Test)
	M±SD/n (%)	M±SD/n (%)	M±SD/n (%)	M±SD/n (%)	
Demographics/Anthropometric measure/Fatigue score					
Age in years (Mean± SD)	39±14	56±6	38±14	35±12	0.052
[a]Weight in pounds (Mean±SD)	163.5±44.5	187.2±18.9	172.6±53.9	143.5±27.6	0.038*
[b]Upper-mid-arm circuference in inches (Mean±SD)	12.4±8.5	13.1±0.9	14.3±11.1	9.5±4.9	0.106
Fatigue serverity scale score (Mean±SD)	31.7±13.6	38.8±13.2	31.7±13.6	29.5±14.2	0.475
Race (%)					0.32
White	24 (70.6)	2 (50.0)	14 (82.4)	8 (61.5)	
Black	6 (17.6)	2 (50.0)	2 (11.8)	2 (15.4)	
Hispanic	2 (5.9)	-	1 (5.9)	1 (7.7)	
Asian	2 (5.9)	-	-	2 (15.4)	
Location (%)					0.162
Urban	29 (85.3)	3 (75.0)	13 (76.5)	13 (100.0)	
Rural	5 (14.7)	1(25.0)	4 (23.5)	-	
SBP					
[c]Office BP	119.3±16.3	132.3±15.3	114.6±9.8	121.2±22.5	0.033*
ABP-24hours	117.8±9.8	127.9±12.6	116.7±9.4	116.1±8.1	0.139
ABP-day	120.3±10.9	130.4±13.9	120.0±10.9	117.7±9.1	0.267
ABP-night	107.2±9.0	117.6±13.0	105.7±7.0	106.1±8.6	0.189
ARV	9.5±2.5	10.2±2.1	9.7±3.0	9.1±1.8	0.667
SV	12.7±3.4	14.1±3.2	12.9±4.2	12.0±2.1	0.581
SD	12.1±3.4	13.3±3.3	12.3±4.1	11.5±2.5	0.595
COV	10.2±2.5	10.3±2.2	10.4±3.1	9.9±1.8	0.884
wSD	10.2±2.6	11.7±2.1	10.2±3.0	9.8±2.2	0.314
Dipping					
<10%	13 (38.2)	1 (25.0)	6 (35.3)	6 (46.2)	0.699
≥10%	21 (61.8)	3 (75.0)	11 (64.7)	7 (53.8)	
DBP					
Office BP*	70.4±14.6	79.0±3.8	71.7±12.8	64.4±18.7	
ABP-24hours	73.3±7.0	79.1±6.6	73.0±6.4	71.8±7.5	0.206
ABP-day	76.1±7.7	81.8±7.1	76.3±7.1	74.2±8.1	0.236
ABP-night	62.0±6.4	68.1±7.4	61.4±5.6	60.8±6.6	0.398
ARV	8.5±2.0	8.8±1.7	8.9±2.4	7.8±1.1	0.514
SV	11.1±2.8	11.8±2.8	11.6±3.6	10.2±1.3	0.631
SD	11.1±2.2	11.3±1.8	11.5±2.5	10.5±1.9	0.453
COV	15.3±3.4	14.3±2.6	15.9±4.1	14.7±2.4	0.807
wSD	9.0±2.1	9.8±0.9	9.3±2.6	8.4±1.8	0.232
Dipping					
<10%	6 (17.6)	1 (25.0)	2 (11.8)	3 (23.1)	0.842
≥10%	28 (82.4)	3 (75.0)	15 (88.2)	10 (35.7)	
ABP measures of arterial stiffness					
AIx@75	22.9±7.1	26.8±10.4	20.9±6.0	24.2±7.2	0.219
PWV	6.2±1.3	8.0±1.1	6.0±1.3	5.7±1.0	0.030*

[a]missing=2; [b]missing=4 ; [c]missing=6 ; *$p < 0.05$

m= mean; SD= standard deviation, BP = blood pressure; ABP = ambulatory blood pressure; ARV= average real variability; SV= successive variation; wSD = weighted standard deviation; AIx@75= augmentation index at heart rate of 75 beat per minute; PWV = pulse wave velocity.

Table 1: Summary of selected demographics, anthropometric measurements, fatigue score, ambulatory blood pressure profiles, and ambulatory blood pressure variability indices, by COVID-19 diagnosis and hospitalization status.

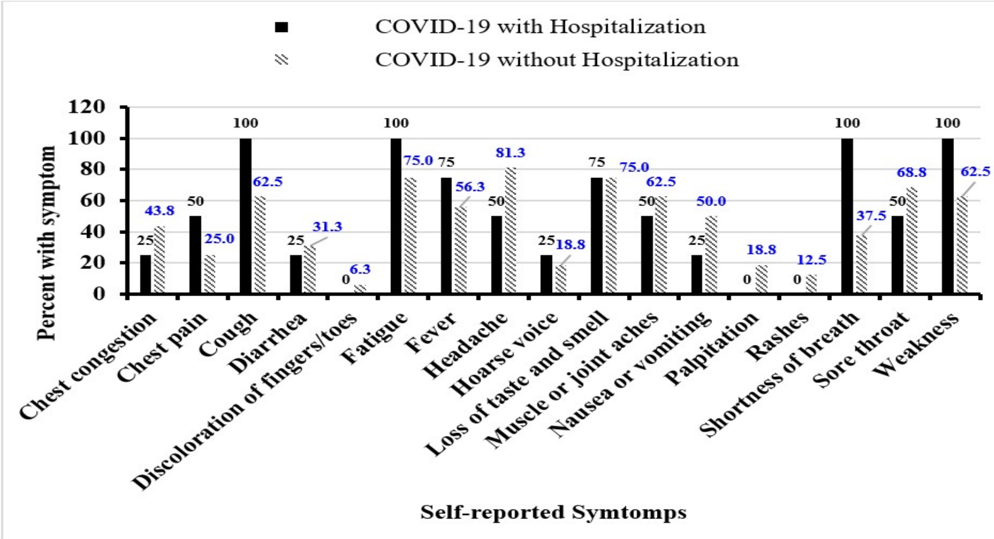

Figure 1: Percentage of patient-reported COVID-19 related symptoms at the time of COVID-19 diagnosis by hospitalization status.

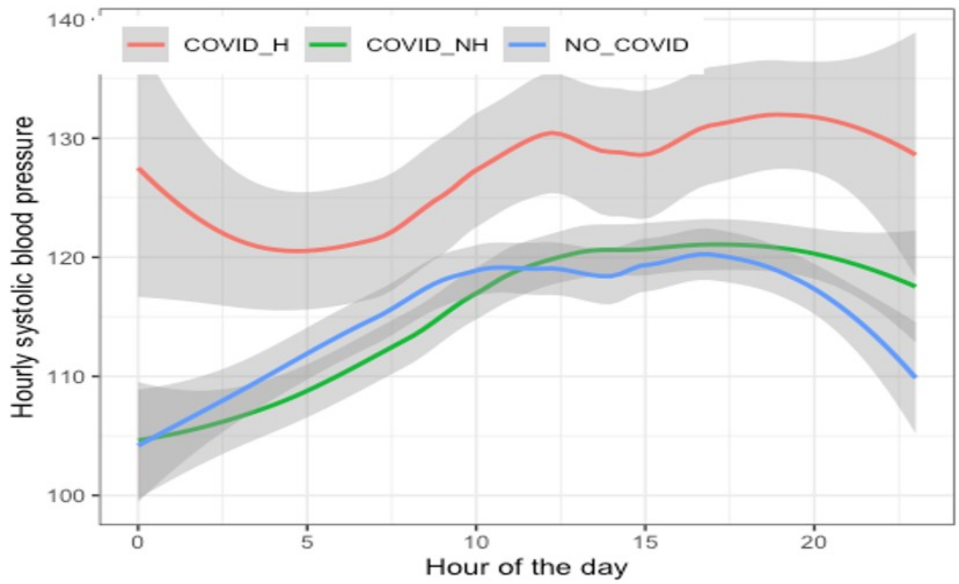

Figure 2a: Distribution of hourly peripheral SBP by COVID-19 diagnosis/hospitalization status during a 24-hour ABP measurement cycle.

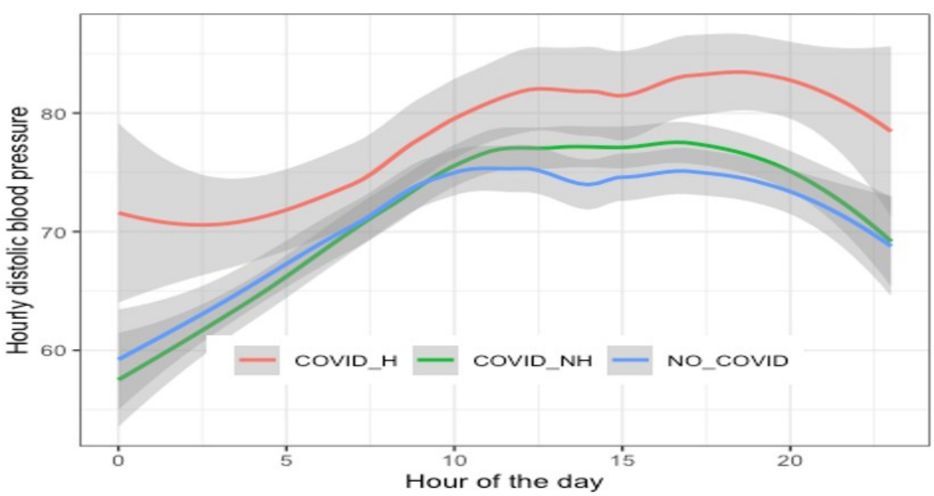

Figure 2b: Distribution of hourly peripheral DBP by COVID-19 diagnosis/hospitalization status during a 24-hour ABP measurement cycle.

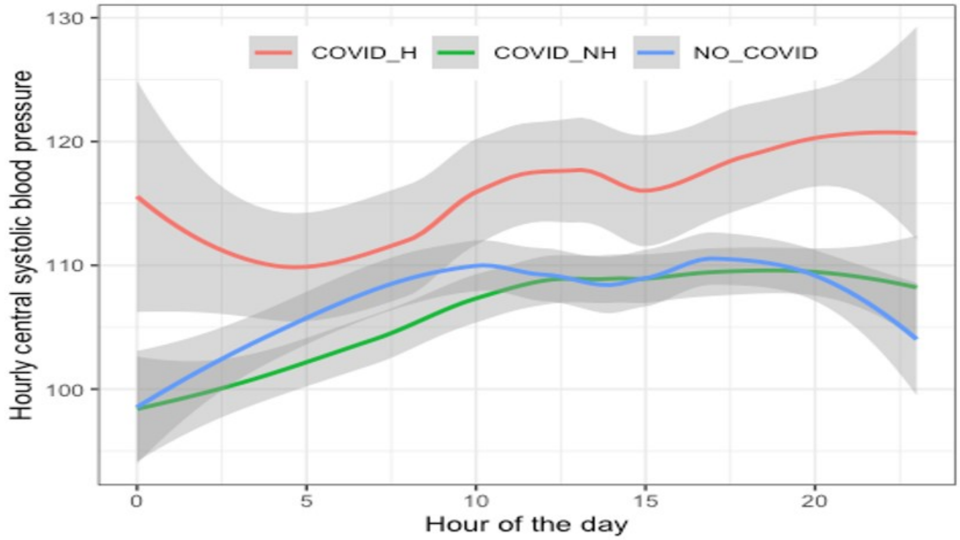

Figure 2c: Distribution of hourly peripheral cSBP by COVID-19 diagnosis/hospitalization status during a 24-hour ABP measurement cycle.

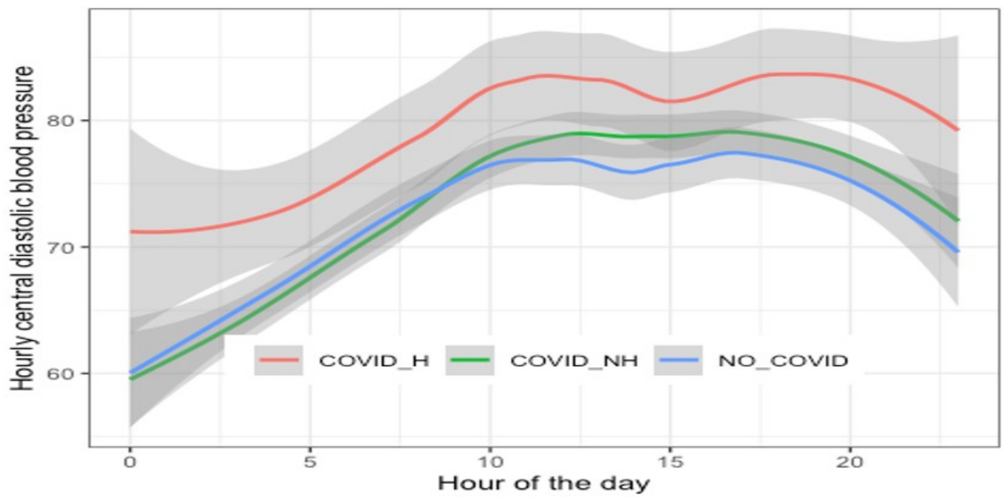

Figure 2d: Distribution of hourly peripheral cDBP by COVID-19 diagnosis/hospitalization status during a 24-hour ABP measurement cycle.

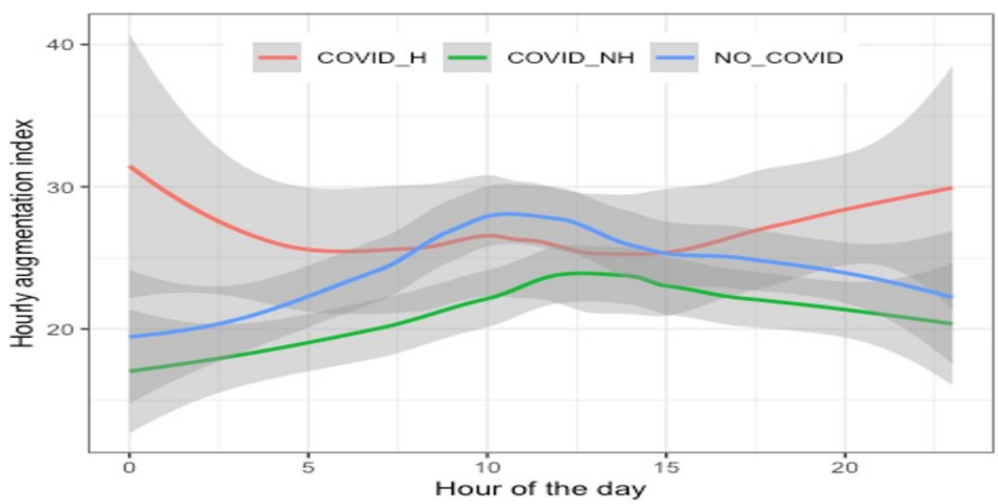

Figure 2e: Distribution of hourly peripheral AIx@75 by COVID-19 diagnosis/hospitalization status during a 24-hour ABP measurement cycle.

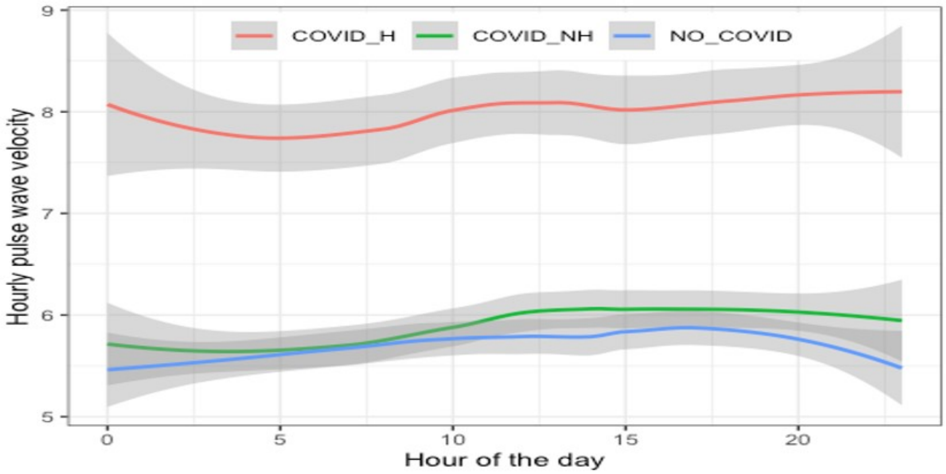

Figure 2f: Distribution of hourly peripheral PWV by COVID-19 diagnosis/hospitalization status during a 24-hour ABP measurement cycle.

Study Group	Dependent Variable					
Study Group	SBP β(SD)	DBPβ(SD)	cSBP β(SD)	cDBP β(SD)	AIx@75 β(SD)	PWV β(SD)
COVID-19 with no hospitalization	-6.33 (6.55)	-5.80 (4.83)	-3.36 (4.59)	-5.10 (4.68)	-4.30* (2.38)	-0.33 (0.34)
No COVID-19	-3.58 (7.16)	-6.35 (6.02)	0.80 (5.37)	-5.60 (5.91)	-3.97 (2.77)	-0.25 (0.31)
Observations	1,110	1,110	1,008	1,008	1,110	1,110
Adjusted R [2]	0.28	0.24	0.25	0.28	0.24	0.87

The reference group is Hospitalization with COVID-19
Notes: Cluster robust standard errors (at 24-hour ABP measurement level) are reported in parenthesis
Model adjusted for covariates (timing of BP [day/night], age, sex, race, smoking, weight, chronic illness) and standard errors; *p<0.1
SBP = systolic blood pressure; DBP= diastolic blood pressure; cSBP = central systolic blood pressure; cDBP= central diastolic blood pressure; AIx@75= augmentation index at heart rate of 75 beat per minute; SD = standard deviation

Table 2: Multiple linear regression results for the association of 24-hour ABP parameters with COVID-19 diagnosis/hospitalization status.

Discussion

This pilot study presents 24-hour ABP parameters in patients with and without the diagnosis of COVID-19. The main findings of the study are: (1) Patients hospitalized with COVID-19 had a different pattern of 24-hour ABP parameters than COVID-19 patients with no hospitalization and those with no COVID-19; (2) COVID-19 patient with hospitalization were, on average, older than those with a COVID-19 diagnosis who were not hospitalized and those with no COVID-19 diagnosis; (3) those with COVID-19-related hospitalization reported more symptoms such as cough, fatigue, fever, hoarse voice, shortness of breath, and weakness compared to those with COVID-19 diagnosis who were not hospitalized. Patients with COVID-19 hospitalization also had a higher fatigue severity score compared to those with COVID-19 who were not hospitalized and those with no COVID-19 diagnosis. Various 24-hour ABP measures, including SBP, DBP, cSBP, cDBP, AIx@75, and PWV, were all higher in COVID-19 patients who were hospitalized compared to those who were not, both during the day and night. The elevated 24-hour ABP measurements in hospitalized COVID-19 patients are consistent with studies indicating that severe COVID-19 can lead to cardiovascular complications [4,11]. However, the specific BP parameters and the extent of elevation may vary between studies, potentially due to differences in patient populations or timing of the measurements. For example, a recent study investigating the impact of COVID-19 on ABP in young adults did not find a difference between COVID-19 patients and controls, but did report higher BP parameters in COVID-19 patients with more recent infection [8]. After adjusting for various factors like day vs. night BP, age, sex, race, smoking, weight, and the presence of chronic illness, patients with COVID-19 diagnosis not resulting in hospitalization had significantly lower AIx@75 compared to those hospitalized with COVID-19. The significant difference in AIx@75 between hospitalized and non-hospitalized COVID-19 patients, even after adjusting for various factors, is a noteworthy finding. It suggests that this parameter may be a potential predictor of the severity of cardiovascular outcomes related to COVID-19. AIx@75 has been previously reported to be associated with increased risk of CVD in hemodialysis patients [23] and improved cardiovascular risk prediction in patients at low cardiovascular risk [24]. A study comparing 24-hour ABP among patients hospitalized with COVID-19 and control groups with known history of hypertension but no history of COVID-19 infection reported significantly higher average 24-hour SBP and DBP, average night times SBP and DBP, and average daytime SBP among those with COVID-19 hospitalization than hypertensive controls with no history of COVID-19 infection. Another study reported increased new-onset non-dipper hypertension in patients with history of COVID-19 hospitalization [11].

In the current study, hospitalized patients with the diagnosis of COVID-19 were, on average, older than those with a COVID-19 diagnosis who were not hospitalized and those with no COVID-19 diagnosis. Other studies have also reported that hospitalized COVID-19 patients tend to be older than non-hospitalized ones [25,26].This finding is consistent with the general understanding that older individuals are at a higher risk of severe disease and hospitalization due to COVID-19.The higher prevalence of symptoms such as cough, fatigue, fever, hoarse voice, shortness of breath, and weakness in hospitalized Covid-19 patients aligns with findings from various studies, emphasizing that severe cases of COVID-19 often present with a more extensive range of symptoms [27,28]. However, the specific symptoms observed may vary across studies.A significant proportion (75%) of COVID-19 patients who were hospitalized reported an illness duration of more than 3 weeks, in contrast to only 37.5% of those not hospitalized. The extended illness duration observed in hospitalized patients, with 75% experiencing more than 3 weeks of illness, is in line with some literature suggesting that severe COVID-19 cases may have a longer recovery period [27,29]. Generally, a fatigue score of 36 or more is a score that indicates severe fatigue and hence warrants further evaluation by a clinician [30].The higher fatigue severity score in hospitalized COVID-19 patients is in line with reports of persistent fatigue as a post-COVID symptom in some individuals [31-33]. The degree of fatigue can differ between studies, possibly due to variations in measurement methods or patient demographics.

Despite being one of the first few studies investigating 24-hour ABP parameters in patients with COVID-19 with different levels of severity, the study has some limitations worth mentioning. The sample size was small, and the study used convenient sampling, potentially limiting the generalizability of the findings. Additionally, the presence and absence of chronic conditions was determined based on self-reporting and therefore is prone to bias. Overall, our findings indicate that individuals hospitalized with COVID-19 exhibit significant differences in terms of age, symptom severity, illness duration, BP measurements, and fatigue severity compared to those with a COVID-19 diagnosis not resulting in hospitalization. The specific significance of these differences, particularly the elevated AIx@75 in the non-hospitalized group after adjusting for covariates and potential correlation, suggests potential implications for clinical management and patient care. Twenty four-hour ABP monitoring profiles, especially AIx@75 might provide an early sign of CVD in patients hospitalized with COVID-19 infection. Our results should serve as preliminary data to help set parameters used in monitoring cardiovascular health post-COVID-19 infection and assist in designing a larger study. ABP monitoring may prove beneficial as a non-invasive approach to predict the long-term cardiovascular effects of COVID-19 infection [8]. A large-scale study is warranted to confirm the findings of our study. In summary, this study contributes to the growing body of literature on COVID-19 by highlighting key differences between hospitalized and non-hospitalized patients, particularly in terms of age, symptoms, illness duration, and 24-hour ABP measurements.

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Registration Number

This study doesn't qualify as a clinical trial and therefore we do not have a registration number

Author's Contributions

MFM and HTH (Conception and design of the study, acquisition of data, analysis and interpretation of data, drafting, revising, and final approval of the article); SA, JM, CP, and JHE (acquisition of data, analysis and interpretation of data, drafting, revising, and final approval of the article)

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Conflict of Interest

All authors report no conflict of interest.

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