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Risk of High Blood Pressure in Hospitalized Patients With COVID- 19: A Serum Marker Study

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Abstract

Objectives: COVID-19 is known as a complex disease with a set of multifaceted disorders in the human body. Several factors such as gender, age, and ethnic background seem to play a major role in the pathogenesis, severity and mortality of the disease. The association between COVID-19 and hypertension has not been fully investigated. In the present study, we aimed to investigate changes in blood pressure (BP) in men and women hospitalized with COVID-19.

Materials and Methods: In this perspective and single-center study, BP, hepatic enzymes and CRP levels of 295 hospitalized COVID-19 patients and 117 healthy men and women were studied.

Results: Elderly and young men and women had higher systolic blood pressure (SBP) and lower diastolic blood pressure (DBP) than age-matched healthy men and women, respectively. Post-menopausal women with COVID-19 had significantly higher SBP than pre-menopausal women within four days of hospitalization. Elderly men with COVID-19 had significantly higher SBP than young men on the second, third and fourth days of hospitalization. Pulse pressure was significantly increased in COVID-19 patients compared with healthy individuals during four days of BP monitoring. Data analysis revealed a positive correlation between SBP and CRP in non- menopausal women and men under 65 years of age on the first day of hospitalization.

Conclusions: There was an increase in SBP and a decrease in DBP in men and women hospitalized with COVID-19 during four days of hospitalization compared with healthy age- matched men and women. COVID-19 significantly increased pulse pressure in all study groups compared to healthy age-matched controls.

Keywords: SARS-CoV-2, Blood pressure, C-reactive protein

Introduction

Coronavirus is known as a clade of beta coronavirus associated with Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) (1), and officially named "SARS-CoV-2" by the World Health Organization (WHO). Available studies have shown a number of potential complications of COVID-19 including inflammation, lung fibrosis, stroke, cardiac thrombosis, and mood disorders (2). Growing evidence has shown that coronavirus can recruit the angiotensin converting enzyme II (ACE2) receptor to enter affected cells (3). ACE2, an integral membrane glycoprotein, is expressed in tissues such as endothelium, kidneys, and heart (4,5) and may play an important role in human blood pressure (BP) regulation (6). Notably, ACE2 expression potentially decreases with age. Accordingly, higher expression of ACE2 has been reported in aged female rats compared to aged males (7). The protective role of estrogen hormone against cardiovascular damage has been proposed in recent years. Estrogen plays an important role in BP regulation through modulation of ACE2 (8). BP is found to be higher in patients with COVID-19 (9). However, little is known about BP in men and women with coronavirus at different ages. Herein, we aimed to investigate BP in young and old women and men hospitalized with COVID-19.

Materials and Methods

Study Design

The present study is a perspective and single-center study on patients with COVID-19. In this study, the database of COVID-19 patients from January 1, 2022 to January 1, 2023, was used. Coronavirus disease was confirmed in patients with the detection of SARS-CoV-2 ribonucleic acid on nasopharyngeal and oropharyngeal swabs using reverse transcriptase polymerase chain reaction in the Microbiology Laboratory of Imam Sajjad hospital according to the guidelines of the WHO (10). Hospitalized COVID-19 patients without history of hypertension were included in the study. Patients with chronic diseases such as cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), chronic liver disease (CLD), asthma, diabetes, dementia, endocrine disorders and cerebrovascular

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Key Messages

- In elderly men and post-menopausal women with COVID-19, higher SBP and lower DBP were observed in comparison to non-COVID-19 age-matched controls. Similarly, young men and women with COVID-19 showed an increase in SBP and decrease in DBP compared to non-COVID-19 age-matched controls. Notably, all hospitalized patients with COVID-19 had a positive CRP assay.

disease were excluded from the study. Smokers, alcohol drinkers and drug addicts were excluded from the study. It should be noted that none of the participants used prescription drugs. After excluding the patients with the mentioned diseases, 295 hospitalized patients with COVID-19 were included in the study and divided into four groups. Pre-menopausal women over 18 years old (group A), menopausal women (confirmed menopause) (group B), men 18- 65 years old (group C), men over 65 years old (group D). Also, 117 Caucasian out-patients of age-matched non-COVID-19 people were included in the study and divided into four groups; Pre-menopausal women over 18 years old (group A`), Menopausal women (confirmed menopause), (group B`), Men 18- 65 years old (group C`), Men over 65 years old (group D`). Body mass index (BMI) of young men and women in control and COVID-19 groups were 23, and 24, respectively. The BMI for elderly men and women were 26, and 28, respectively.

Data Collection

Clinical findings were extracted from the medical records of the patients. Three researchers performed a manual record review to organize and verify the data. The dataset included laboratory tests and BP records of patients. BP was measured 4 times on the upper right arm by a trained nurse with a sphygmomanometer after 15 minutes of rest. Patients' BP was measured four times; morning (6 AM), 12 noon, evening (6 PM) and 12 midnight. It is worth nothing that BP higher than 140/90 mm Hg for three consecutive days was considered as high BP (11, 12). Clinical symptoms and laboratory values including C-reactive protein (CRP), alanine transaminase (ALT) and aspartate transaminase (AST), alkaline phosphatase (ALP) levels were measured at admission or immediately after admission. Qualitative diagnosis of CRP was performed using PCR Latex test based on the presence of visible agglutination in the sample (REF CSAD87027). According to the intensity of agglutination latex particles, CRP levels were reported as weakly positive, one, two and three positives. The normal reference intervals for AST, ALT and ALP were (< 31 U/L), 0–41 U/L, and (100–320 U/L), respectively.

Statistical Analysis

Data are expressed as mean ± standard error. Kruskal–Wallis test and Dunn's post hoc test was used for comparison the data in the study groups. Pearson's correlation coefficient test (two-tailed) was performed to assess the correlation between CRP, BP and hepatic enzymes. Statistical data was analyzed using IBM SPSS software (version 23). A value of $P < 0.05$ was considered statistically significant.

Results

Systolic and Diastolic Blood Pressure in Hospitalized Women for COVID-19

Blood pressure and relevant markers of 123 confirmed COVID-19 women were analyzed. Post-menopausal women had higher SBP than pre-menopausal women during four days of hospitalization ($P<0.05$). DBP in post-menopausal women was significantly higher than pre-menopausal women on the 1st, 2nd and 3rd days of hospitalization ($P<0.05$).

The SBP of non-menopausal women (group A) was on the first, second, third and fourth days of hospitalization; 113.39 ± 0.8, 112.02 ± 0.80, 111.82 ± 0.89, and 112.5 ± 0.94, respectively. Also, the

SBP of post-menopausal women (group B) during four days of hospitalization was 119.24 ± 1.7, 118.39 ± 1.58, 119.04 ± 1.77, and 119.34 ± 1.98, respectively.

DBP of non-menopausal women (group A) was on the first, second, third and fourth days of hospitalization; 71.76 ± 0.56, 70.23 ± 0.60, 70.42 ± 0.61, and 71.39 ± 0.51, respectively. Also, DBP of women in the B group during four days of hospitalization was 74.19 ± 1.09, 74.14 ± 1.13, 74.22±1.10, and 73.17 ± 1.27, respectively (Table 1), (Figures 1 and 2; panels a, b, e, and f).

Systolic and Diastolic Blood Pressure in Hospitalized Men for COVID-19

Blood pressure and relevant markers of 172 confirmed COVID-19 men aged 18 years and older were studied. SBP was higher in old men compared to men in group C on the second, third and fourth days of hospitalization ($P<0.05$). The SBP of group C men was on the first, second, third and fourth days of hospitalization; 115.40 ± 0.61, 115.25 ± 0.67, 114.74 ± 0.70, 114.05 ± 0.70, respectively.

The SBP of men in group D on the first, second, third and fourth days of hospitalization was 116.81 ± 1.65, 118.42 ± 1.69, 122.13 ± 2.64, and 121.22 ± 2.65, respectively. Men in group D had higher DBP compared to men in group C, but it was not statistically significant. DBP of group C men on the first, second, third and fourth days of hospitalization was; 72.22 ± 0.50, 72.69 ± 0.54, 72.66 ± 0.55, and 71.98 ± 0.69, respectively. DBP of D group men during four days of hospitalization was 73.32 ± 1.05, 73.94 ± 1.14, 74.03 ± 1.13, and 73.66 ± 1.15, respectively (Table 2, Figures 1 and 2; panels c, d, g, and h).

Comparison of SBP and DBP in Healthy and Hospitalized Women With COVID-19

Pre-menopausal women with COVID-19 had higher SBP and lower DBP than healthy pre-menopausal women

Table 1. Mean SBP and DBP in Pre-menopausal and Post-menopausal Women With COVID-19

Blood Pressure	Pre-menopause (Group A)				Post-menopause (Group B)			
	Minimum	Maximum	Mean	Std. Error	Minimum	Maximum	Mean	Std. Error
Systole (First day)	97.75	136.75	113.39	0.80	91.25	141.6	119.24	1.70
Systole (Second day)	100	142.75	112.02	0.80	102.25	144	118.39	1.58
Systole (Third day)	97.5	146.25	111.82	0.89	100	140	119.04	1.77
Systole (Fourth day)	96	141.25	112.50	0.94	102.5	140	119.34	1.98
Diastole (First day)	61.5	87.5	71.76	0.56	58.75	85	74.19	1.09
Diastole (Second day)	54.5	85	70.23	0.60	63.3	93.3	74.14	1.13
Diastole (Third day)	57	82.5	70.42	0.61	60	87.50	74.22	1.10
Diastole (Fourth day)	62.5	81.25	71.39	0.51	55	81.25	73.17	1.27

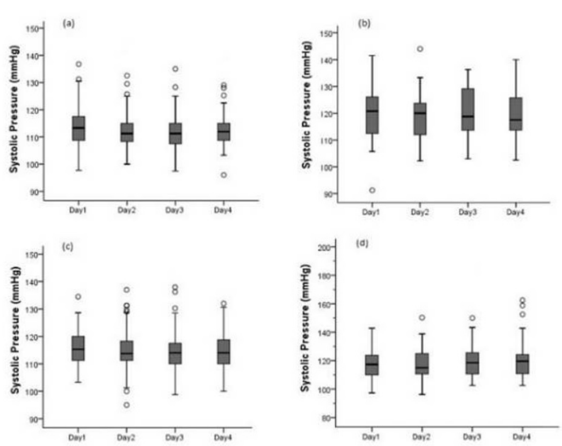

Figure 1. Systolic Blood Pressure in the Studied Groups. Systolic pressure during hospitalization; Pre- menopausal women (a), Post- menopausal women (b), Men younger than 65 years (c), old men (d),

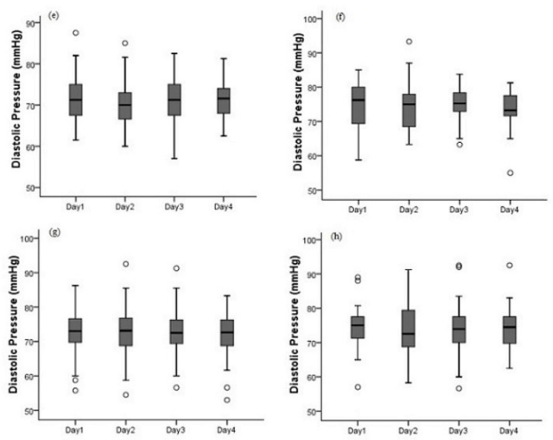

Figure 2. Diastolic Blood Pressure in the Studied Groups. Pre- menopausal women (e), Post-menopausal women (f), Men younger than 65 years (g), old men (h).

during four days of BP monitoring. The SBP of non-menopausal women with COVID-19 was significantly higher than healthy non- menopausal women on the first day of BP monitoring ($P < 0.05$). The SBP of healthy non-menopausal women (group A`) was on the first, second, third and fourth days of hospitalization; 109.12 ± 1.24, 110.16 ± 1.32, 110.14 ± 1.38, and111.19 ± 1.50, respectively. COVID-19 increased SBP in post-menopausal women compared to healthy post-menopausal women during four days of BP monitoring.

The SBP in post-menopausal women with COVID-19 was significantly higher than healthy post-menopausal women on 1st, and 3rd days of BP monitoring ($P < 0.05$). SBP of healthy post-menopausal women (group B`) during four days of hospitalization was; 114.20 ± 1.17, 117.32 ± 0.95, 114.87 ± 1.08, and 116.95 ± 1.11, respectively.

COVID-19 meaningfully decreased DBP in non-menopausal and post-menopausal women during

Table 2. Mean SBP and DBP Among Men Younger and Older Than 65 Years With COVID-19

Blood Pressure	Men at Age 18-65 Years Old (Group C)				Men Older Than 65 Years Old (Group D)			
	Minimum	Maximum	Mean	Std. Error	Minimum	Maximum	Mean	Std. Error
Systole (First day)	102.5	134.5	115.40	0.61	92.3	143.75	116.81	1.65
Systole (Second day)	95	137	115.27	0.67	96.25	150.25	118.42	1.69
Systole (Third day)	98.75	140.5	114.74	0.70	102.5	185	122.13	2.64
Systole (Fourth day)	100	132	114.05	0.70	102.5	162.5	121.22	2.65
Diastole (First day)	55.75	86.25	72.22	0.50	51.5	89	73.32	1.05
Diastole (Second day)	54.5	92.5	72.69	0.54	51.25	91.25	73.94	1.14
Diastole (Third day)	56.6	91.25	72.66	0.55	56.6	92.5	74.03	1.13
Diastole (Fourth day)	53	83.3	71.98	0.69	62.5	92.5	73.66	1.15

four days of hospitalization compared to healthy age-matched controls. DBP of non- menopausal women with COVID-19 was lower than healthy non- menopausal women on the second, third and fourth days of BP monitoring ($P<0.05$). DBP of post-menopausal women with COVID-19 was lower than healthy post-menopausal women on the second and fourth days of BP monitoring ($P<0.05$).

DBP of healthy non-menopausal women (group A`) was on the first, second, third and fourth days of BP monitoring; 73.82 ± 1.42, 73.65 ± 1.31, 74.59 ± 1.14, and 74.73 ± 1.54, respectively. Also, DBP of women in the B` group during four days of BP monitoring was; 76.03 ± 1.22, 77.63 ± 1.48, 76.24 ± 1.38, and 77.13 ± 1.46, respectively (Table 3) (Figures 3 and 4; Panels a`, b`, e`, and f`).

Comparison of SBP and DBP in Healthy and Hospitalized Men With COVID-19

COVID-19 significantly increased SBP in elderly men (group D) compared with healthy elderly men (group D`) during four days of BP monitoring ($P<0.05$). The SBP of healthy elderly men on the first, second, third and fourth days of BP monitoring was; 113.54 ± 1.11, 114.84 ± 0.92, 116.50±0.78, and 117.10 ± 0.94, respectively. The SBP of young men with COVID-19 (group C) was higher than healthy young men (group C`) on the first and second days of BP monitoring ($P<0.05$).

The SBP of healthy young men (Group C`) on the first, second, third and fourth days of hospitalization was 112.98 ± 1.16, 112.74 ± 1.10, 115.10 ± 0.87, 114.88 ± 0.82, respectively. COVID-19 significantly decreased DBP in young men (group C) compared with healthy young men (group C`) during four days of BP monitoring ($P<0.05$). DBP of healthy young men (group C`) was on the first, second, third and fourth days of BP monitoring; 76.51 ± 0.84, 79.45 ± 0.75, 80.72 ± 1.22, 78.37 ± 0.77, respectively. COVID-19 significantly decreased DBP in elderly men (group D) compared with healthy elderly men (group D`) during four days of BP monitoring ($P<0.05$). DBP of healthy elderly men (group D`) was on the first, second, third and fourth days of BP monitoring; 78.28 ± 0.58, 79.09 ± 0.73, 80.77 ± 0.82, and 79.85 ± 0.69, respectively (Table 4) (Figures 3 and 4; Panels c`, d`, g`, and h`).

Pulse Pressure in Confirmed-COVID-19 Patients

There was a significant difference in pulse pressure between group A and group B patients during hospitalization ($P<0.05$). The pulse pressure of young women with COVID-19 (group A) on the first, second, third, and fourth days of hospitalization was 41.76 ± 0.59, 42.02 ± 0.57, 41.36 ± 0.56, and 40.36 ± 0.96, respectively. The pulse pressure of post-menopausal women (group B) on the first, second, third, and fourth days of hospitalization was 45.29 ± 1.11, 43.95 ± 0.90, 44.45 ± 1.05, and 46.17 ± 1.94, respectively.

There was a significant difference in pulse pressure between group C and group D patients on the second,

Table 3. Mean SBP and DBP in Healthy Pre-menopausal and Post-menopausal Women

Blood Pressure	Pre-menopause (Group A`)				Post-menopause (Group B`)			
	Minimum	Maximum	Mean	Std. Error	Minimum	Maximum	Mean	Std. Error
Systole (First day)	96	119	109.12	1.24	102.5	123.75	114.20	1.17
Systole (Second day)	95.72	102.33	110.16	1.32	106.6	123.33	117.32	0.95
Systole (Third day)	95	122	110.14	1.38	102	123.75	114.87	1.08
Systole (Fourth day)	86	124.66	111.19	1.50	105	125.25	116.95	1.11
Diastole (First day)	58.25	87.66	73.82	1.42	62.50	85	76.03	1.22
Diastole (Second day)	58	86	73.65	1.31	59	95	77.63	1.48
Diastole (Third day)	61.6	85.3	74.59	1.14	60	85	76.24	1.38
Diastole (Fourth day)	56	93.3	74.73	1.54	60	87.75	77.13	1.46

Table 4. Mean SBP and DBP Healthy Men Younger and Older Than 65 Years

Blood Pressure	Men at Age 18-65 Years Old (Group C`)				Men Older Than 65 Years Old (Group D`)			
	Minimum	Maximum	Mean	Std. Error	Minimum	Maximum	Mean	Std. Error
Systole (First day)	103	121.25	112.98	1.16	105	125	113.54	1.11
Systole (Second day)	105	121.25	112.74	1.10	105	123.75	114.84	0.92
Systole (Third day)	108	124.25	115.10	0.87	103.75	122.5	116.05	0.78
Systole (Fourth day)	108	120.60	114.88	0.82	105	130	117.10	0.94
Diastole (First day)	68.25	84.75	76.51	0.84	71.66	86.25	78.28	0.58
Diastole (Second day)	63.75	85	79.45	0.75	72.5	88.33	79.09	0.73
Diastole (Third day)	66.25	94	80.72	1.22	74.5	90	80.77	0.82
Diastole (Fourth day)	66	86.66	78.37	0.77	75	86.25	79.85	0.69

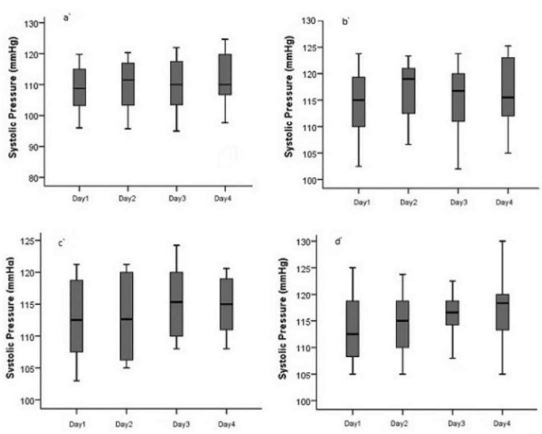

Figure 3. Systolic Pressure in Healthy Controls. Pre- menopausal women (a`), Post- menopausal women (b`), Men younger than 65 years (c`), old men (d`).

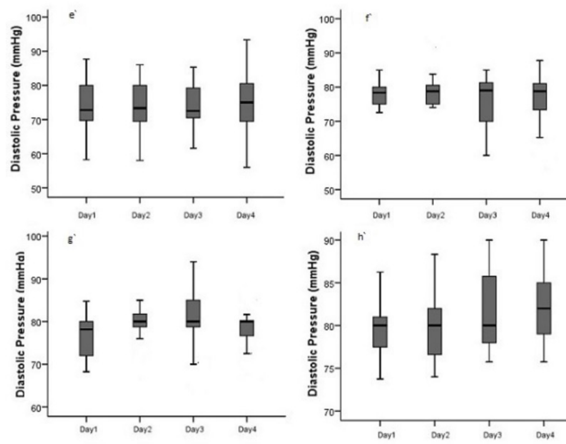

Figure 4. Diastolic Blood Pressure in Healthy Controls. Pre- menopausal women (e`), Post-menopausal women (f`), Men younger than 65 years (g`), old men (h`)

third and fourth days of BP monitoring ($P<0.05$). The average pulse pressure of group C men on the first, second, third, and fourth days of hospitalization was 43.45 ± 0.52, 42.74 ± 0.57, 42.03 ± 0.44, and 42.16 ± 0.44, respectively. Also, the average pulse pressure of group D men on the first, second, third, and fourth days of hospitalization was 43.82 ± 1.13, 44.97 ± 1.22, 48.90 ± 2.34, and 46.98 ± 2.05, respectively (Table 5, Figure 5 k, L).

Comparison of Pulse Pressure in Healthy and Hospitalized Patients With COVID-19

COVID-19 significantly increased pulse pressure in pre-menopausal women compared with healthy non-menopausal women during four days of BP monitoring ($P<0.05$). The pulse pressure of healthy non-menopausal women on the first, second, third and fourth days of BP monitoring was 35.30 ± 1.01, 36.50 ± 1.07, 35.55 ± 0.93, and 36.45 ± 1.20, respectively.

Post-menopausal women with COVID-19 had higher pulse pressure than healthy post-menopausal women during four days of BP monitoring ($P<0.05$). The pulse pressure of healthy post-menopausal women on the first, second, third and fourth days of BP monitoring was 38.17 ± 0.76, 39.69 ± 1.80, 38.62±1.28, and 39.82 ± 1.09, respectively.

COVID-19 significantly increased pulse pressure in young men compared with healthy young men during four days of BP monitoring ($P<0.05$). Also, elderly men with

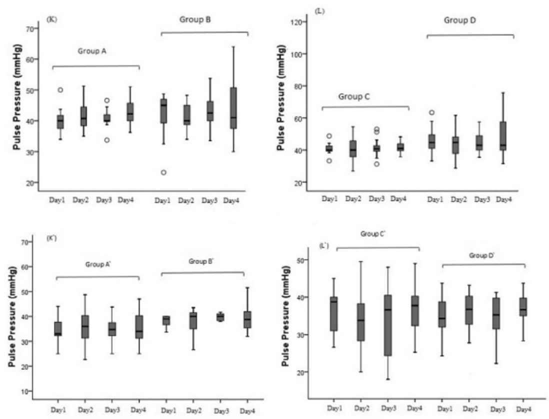

Figure 5. Pulse Pressure in the Studied Groups. Pre-menopausal women and post-menopausal women (Group A, B) (k), Men younger than 65 years and old men (Group C, D) (L), Healthy Pre-menopausal women and post-menopausal women (Group A`, B`) (k`), Healthy men younger than 65 years and old men (Group C`, D`) (L`).

COVID-19 had higher pulse pressure levels compared to healthy elderly men during BP monitoring ($P<0.05$). The pulse pressure of healthy young men on the first, second, third and fourth days of BP monitoring was 36.47 ± 1.02, 33.29 ± 1.39, 34.38 ± 1.68, and 36.51 ± 1.12, respectively. The pulse pressure of healthy elderly men on the first, second, third and fourth days of BP monitoring was 35.26 ± 0.96, 35.75 ± 1.01, 35.27 ± 0.99, and 37.24 ± 0.86, respectively (Table 6, Figure 5 k`, L`).

Table 5. Mean Pulse Pressure in Men and Women With COVID-19

Mean Pulse Pressure	First Day	Second Day	Third Day	Fourth Day
Pre-menopause	41.76± 0.59	42.02± 0.57	41.36± 0.56	40.36± 0.96
Post-menopause	45.29± 1.11	43.95± 0.90	44.45± 1.05	46.17± 1.94
Men younger than 65 years	43.45± 0.52	42.74± 0.57	42.03± 0.44	42.16± 0.44
Men older than 65 years	43.82± 1.13	44.97± 1.22	48.90± 2.34	46.98± 2.05

CRP Levels in the Studied Groups

Positive CRP assay was observed in 79 (92%), 43 (86%), 113 (91 %), and 46 (96%) of groups A, B, C, and D, respectively. There was a weak positive correlation between SBP (first day) and CRP in Groups A and C (Pearson correlation: 0.07 and 0.03, respectively). The data showed that there is a relatively weak positive correlation between CRP and pulse pressure in the A group (first day) (Pearson correlation: 0.16). Also, the data showed that there is a positive correlation between CRP and DBP (first day) in groups B and C (Pearson correlation: 0.03, and 0.10, respectively).

Liver Enzymes (AST, ALT, and ALP) Levels in Hospitalized Patients With COVID-19

The average concentrations of AST, ALT and ALP in group A were 79.54 ± 29.52, 50.78 ± 7.23, and 194.30 ± 9.82, respectively, and the mean concentration of enzymes in group B were 47.71±4.9, 32.37 ± 5.14 and 203.500 ± 16.62, respectively. The average concentration of AST, ALT and ALP in group C was 48.57 ± 4.01, 56.11 ± 7.31, and 193.81 ± 9.64, respectively. Men over 65 years of age had higher mean AST and ALT concentrations. The concentration of these enzymes in group D was 66.03 ± 14.21, 47.91 ± 9.08, and 234.92 ± 20.99, respectively.

Data analysis showed higher AST levels in pre-menopausal women compared to post-menopausal women. Pre-menopausal women had higher ALT levels than post-menopausal women ($P < 0.05$). Also, men in group D had higher levels of AST than men in group C. ALT levels was higher in men of group C compared to elderly men of group D. There was not significant difference in ALP levels between women in groups A, B and men in group C. Data analysis showed higher ALP levels in elderly men compared to young men in group C ($P < 0.05$) (Table 7).

Correlation of AST, ALT and ALP Levels With Blood Pressure in the Studied Groups

There was a positive correlation between SBP (first day) and AST levels in group A (Pearson correlation: 0.20). We found a weak positive correlation between AST and DBP (first day) in Group A (Pearson correlation: 0.06). There was a weak positive correlation between SBP and DBP (first day with ALT levels in group B (Pearson correlation: 0.10, 0.01, respectively). Also, Pearson correlation for ALP and SBP (first day) in group B was 0.05. We found a weak positive correlation between SBP and DBP (first day) with AST levels in Group C (Pearson correlation: 0.06, 0.07, respectively). Also, Pearson correlation for SBP and DBP (first day) with ALT in group C was 0.11, 0.2, respectively).

Data analysis in elderly men showed a positive correlation between SBP and DBP (first ray) with AST levels (Pearson correlation: 0.02, 0.1, respectively). Group C and D men showed a weak correlation for ALP and SBP (first day) (Pearson correlation: 0.10, 0.04, respectively). There was a positive correlation between DBP (first day) and ALP in group C (Pearson correlation: 0.1).

Discussion

The present study highlights age and gender differences in the clinical manifestations of COVID-19 in adult patients hospitalized with COVID-19. The main finding of this study is that the manifestation of COVID-19 at different ages was not similar in men and women. In our study, hospitalized men over sixty-five years of age had higher SBP and DBP than men under sixty-five years of age. Post- menopausal women had higher SBP and DBP than pre-menopausal women. Notably, data analysis revealed higher pulse pressure in older men and post-menopausal women compared to young men and pre-menopausal women, respectively.

COVID-19 meaningfully increased SBP in all study groups compared with age- matched controls. Older men and women had higher SBP and lower DBP than healthy older men and women during four days of BP monitoring. The SBP was elevated in young men and women with COVID-19 compared to healthy young men and women, respectively. COVID-19 significantly increased pulse pressure in all patients compared with age- matched

Table 6. Mean Pulse Pressure in Healthy Men and Women

Mean Pulse Pressure	First Day	Second Day	Third Day	Fourth Day
Pre- menopause	35.30± 1.01	36.50± 1.07	35.55± 0.93	36.45± 1.20
Post- menopause	38.17± 0.76	39.69± 1.80	38.62± 1.28	39.82± 1.09
Men younger than 65 years	36.47± 1.02	33.29± 1.39	34.38± 1.68	36.51± 1.12
Men older than 65 years	35.26± 0.96	35.75± 1.01	35.27± 0.99	37.24± 0.86

Table 7. Liver Enzyme Tests in Men and Women With COVID-19

Liver Enzymes	AST	ALT	ALP
Pre-menopause	79.54± 29.52	50.78± 7.23	194.30± 9.82
Post-menopause	47.71± 4.9	32.37± 5.14	203.500± 16.62
Men younger than 65 years	48.57± 4.01	56.11± 7.31	193.81± 9.64
Men older than 65 years	66.03± 14.21	47.91± 9.08	234.92± 20.79

healthy controls during four days of BP monitoring.

Hypertension has been suggested as the most prevalent comorbidity in COVID-19 patients, in Wuhan, with a prevalence rate of 15.0% to 36.5% (13, 14). Previous studies have shown a higher incidence of hypertension in patients with severe COVID-19. It has been shown that the prevalence of hypertension is higher in deceased patients of COVID-19; 34.0%, vs. the patients who were discharged alive; 28.0% (15). Zhang et al reported that hypertension was associated with an increased risk of mortality after adjusting for gender and age in COVID-19 patients (16).

The mechanisms linking COVID-19 and hypertension are not fully elucidated, but could be related to an imbalance of renin-angiotensin system (RAS), endothelial dysfunction, and a pro- inflammatory state that includes higher levels of cytokines, chemokines and angiotensin II (17). Activation of RAS axis and down-regulation of ACE2/Ang1 are known as possible underlying factors leading to severe conditions of COVID-19 (18,19). ACE2 is suggested to play an important role in the inflammatory immune response in patients with COVID-19 (20). ACE2, which is expressed on capillary endothelial and alveolar epithelial cells, plays an important role in stablishing and modulating BP homeostasis (21).

The upregulation of ACE2 receptor has been exploited by coronavirus as the main route of cell entry and infection. It has been proposed that SARS-CoV-2 downregulates ACE2 through the binding of viral proteins to the ACE2 receptor, thus preventing the normal function of ACE2 and reducing ACE2 expression (20).

Men appear to be at greater risk mortality from COVID-19 regardless of age (22). Swärd et al have reported higher serum levels of membrane-bound angiotensin-converting enzyme 2 (mACE2) in adults and men than in children and female, respectively (23). There are conflicting reports regarding ACE2 expression in men and women with COVID-19. Gagliardi et al. have reported that genetic and hormonal factors can cause over-expression of ACE2 in women with COVID-19 (24).

Estrogen, as a sex hormone, has been shown to play a pivotal role in suppressing the replication of SARS-CoV-2 (25). Specifically, estrogen exerts anti-oxidative and anti-inflammatory effects on the RAS. Interestingly, estrogen can upregulate ACE2 expression in elderly men. (26). In the present study, men under sixty-five years of age had higher SBP and DBP than pre-menopausal women. Nevertheless, the data showed a gradual decrease in SBP during hospitalization in men younger than 65 years.

Estrogen treatment has been reported to have regionally heterogeneous effects on vasomotor function in estrogen-deficient rats (27). Estrogen therapy was shown to increase aortic stiffness and induce endothelial vasodilation in the hindquarters in ovariectomized rat (28). In our study, pre-menopausal women experienced more diastolic and systolic changes than post-menopausal women during hospitalization.

The most severe cases of COVID-19 have been reported in elderly patients (28). Post- menopausal women with COVID-19 are at higher risk for mortality (12.8%) compared to pre-menopausal women (8.6%), suggesting a protective role of estrogen hormone against COVID-19 (29).

Estrogen treatment has been associated with a small reduction in BP in post-menopausal women (30). Contradictory, post-menopausal hypertension was suggested to be due to enhanced BMI rather than ovarian failure (31). More importantly, estrogen treatment has been accompanied by a reduction in SBP and DBP in postmenopausal hypertensive women (32).

In the present study, post-menopausal women had higher SBP and DBP than pre-menopausal women. Also, our data showed a higher pulse pressure in post-menopausal women than in pre-menopausal women during hospitalization. It is worth mentioning that menopausal women had higher systolic pressure and lower diastolic pressure on the fourth day of hospitalization than on the first day of hospitalization. A higher SBP with normal or lower DBP has been associated with higher risk of CVD (33). It has been reported that endothelial dysfunction can increase arterial stiffness, leading to increased systolic pressure and decreased diastolic pressure in elderly patients (34).

ACE2 expression has been shown to be significantly upregulated with age in the setting of alveolar destruction (35). Available reports have indicated that androgens can increase BP through the renin-angiotensin system. Huisman et al. have shown that testosterone levels are increased in hypertensive men and women compared to the normotensives (36). Accordingly, increased SBP and renin activity have been observed in women with high testosterone levels (36).

There are conflicting reports on the role of testosterone on BP in men and women. Testosterone supplement has been shown to exert different effects on male depending on age, metabolic and cardiovascular status (37). Testosterone treatment has been found to decrease mean arterial pressure (MAP) in aged, but increased in young rats, suggesting that this mechanism is partially involved by activation of the renin-angiotensin system (37). A growing body of evidence suggests that viral infection may reduce testosterone production and decreased testosterone levels are associated with severe clinical conditions (38,39).

Montano et al. have indicated that men over 65 years of age with COVID-19 have lower testosterone levels and higher mortality compared to younger men (40). ACE2, expressing on Sertoli and Leydig cells, play an important role in steroidogenesis and spermatogenesis. Notably, it was found that COVID-19 alters testosterone production and testicular function through binding to ACE2 receptors (41).

In the present study, we found a weak correlation between CRP and SBP in young men and women on the first day of hospitalization. A significant increase in CRP levels has been observed in patients with COVID-19 (28), which is recognized as an important marker in severe COVID-19 patients. CRP, a protein produced by the liver, which acts as early marker of inflammation and infection (42). Available studies have suggested that higher BP correlates with higher CRP levels (43,44). Specifically, CRP has been found to be a mediator of vascular disease (45), which can impair endothelial function and cause hypertension (46,47). There are conflicting reports on the role of CRP in hypertension. Smith et al reported that increase in CRP levels does not lead to increase in BP (48).

Serum level of CRP was suggested to be affected by several factors including gender, age, BP, body-mass index, sleep deprivation and insulin resistance (49). CRP was found to be associated with vascular stiffness, cardiovascular events and organ damage (49). Xie et al revealed that patients with low oxygen intake (SpO2 ≤ 90%) had significantly higher CRP levels, suggesting that patients with severe lung injury have increased CRP levels (50).

Available studies have indicated that systemic inflammation may play a pivotal role in the progression and pathogenesis of hypertension (17). Higher levels of circulating CRP were suggested to be associated with a higher risk of hypertension (51). In our study, more than 85% of women and 90% of men with COVID-19 had higher CRP levels on the first day of hospitalization.

Our data showed elevated SBP in COVID-19 patients compared to healthy uninfected individuals. In the present study, elderly and young men and women with COVID-19 had higher SBP and lower DBP than healthy men and women, respectively. Available studies have shown a correlation between arterial stiffness and inflammation, indicating higher arterial stiffness in patients with chronic inflammatory diseases than in the control groups (52). Of note, endothelial damage associated with COVID-19 is found to cause inflammation, thrombosis and dysregulating vascular tone, causing edema and leading to structural and functional arterial remodeling (53).

Increased concentration of liver enzymes has been associated with higher levels of CRP (54). Accordingly, individuals with higher ALT and ALP levels have higher CRP concentration. Notably, increased AST and ALP levels have been reported in hypertensive men and women (54).

Available studies have shown liver damage in COVID-19 patients. SARS-CoV-2 binds to hepatocyte ACE2 (55) and induces hepatocyte swelling, lobular inflammation and cell apoptosis (56). Few clinical trials have been conducted to evaluate the relationship between liver enzymes and BP in men and women. Khalili et al highlighted a potential direct relationship between hepatic serum levels and hypertension (57).

ALT concentration has been suggested as a hepatocyte marker. In our study, older men and women with COVID-19 had lower ALT levels than younger age-matched individuals. Lin et al reported that ALT concentration was negatively correlated with SBP variability in young men (58). Zhu et al have shown that serum levels of ALT, but not AST, are positively associated with hypertension in young men and women (59). In the present study, except for post-menopausal women, serum AST level had a positive correlation with BP in the studied groups. Notably, pre-menopausal women and older men with higher AST levels showed greater systolic changes during hospitalization.

Rahman et al have suggested higher levels ALP in hypertensive adults than normotensive ones (60). However, they did not find a significant association between ALP levels and hypertension (60). Endothelium was suggested as a primary target for higher ALP levels. Emerging evidence from recent studies suggest that there is a significant inverse relationship between ALP concentrations and endothelium-dependent vasodilation (61), suggesting an important role of ALP in vascular stiffness.

Importantly, abnormal ALP activity has been shown in COVID-19 patients (62). It appears that abnormal levels of ALP may be associated with the replication of coronavirus in the liver (62). Gan et al have reported that liver function indexes, including AST, ALT, and ALP can be significantly correlated with oxygenation index (63). Therefore, abnormal liver activity in COVID-19 patients may be related to hepatocyte ischemia.

Available studies have indicated that ALP levels can be related to the reduction of nitric oxide (NO) bioavailability in endothelial cells (64). Taken together, endothelial dysfunction associated with increased ALP levels may play a pivotal role in the pathogenesis of hypertension. In our study, elderly men and post-menopausal women had higher ALP levels than young men and women, respectively.

Our data only showed a positive correlation between SBP but not DBP, and ALP levels in post-menopausal women and elderly men. Overall, the number of patients in the present study was limited. All findings need to be confirmed in further studies.

Limitations of the Study

The study assessed the BP of hospitalized patients and non-COVID-19 individuals manually, which was found to be a main limitation. To improve accuracy, continuous Holter monitoring should be considered. Additionally, due to the short-term nature of the research training, the sample size was limited.

Conclusions

Our data showed an adverse effect of COVID-19 on SBP and DBP in hospitalized men and women. Elderly men and post-menopausal women with COVID-19 experienced higher SBP and lower DBP compared to healthy age-matched groups during four days of BP monitoring. COVID-19 increased SBP and decreased DBP in young men and women compared to healthy age-matched controls. COVID-19 significantly increased pulse pressure in young men and non- menopausal women compared to age- matched controls. Pulse pressure was significantly higher in elderly men and post-menopausal women than healthy elderly men and post-menopausal women during four days of BP monitoring.

Authors' Contribution

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Conflict of Interests

None.

Ethical Issues

The study was approved by the ethics committee of Tabriz Islamic Azad University of Medical Sciences. (code number: IR.IAU.TABRIZ.REC.1401.050).

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