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Risk of hospitalization and mortality associated with uncontrolled blood pressure in patients with hypertension and COVID-19

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ABSTRACT

Objective: The role of uncontrolled blood pressure (BP) in COVID-19 severity among patients with hypertension is unclear. We evaluated the association between uncontrolled BP and the risk of hospitalization and/or mortality in patients with hypertension from a large US integrated healthcare system.
Methods: We identified patients with hypertension and a positive RT-PCR test result or a diagnosis of COVID-19 between March 1 – September 1, 2020 from Kaiser Permanente Southern California. BP categories was defined using the most recent outpatient BP measurement during 12 months prior to COVID-19 infection. The primary outcome of interest was all-cause hospitalization or mortality within 30 days from COVID-19 infection.
Results: Among 12,548 patients with hypertension and COVID-19 (mean age = 60 years, 47% male), 63% had uncontrolled BP (≥130/80 mm Hg) prior to COVID-19. Twenty-one percent were hospitalized or died within 30 days of COVID-19 infection. Uncontrolled BP was not associated with higher hospitalization or mortality (adjusted rate ratios for BP ≥ 160/100 mm Hg vs < 130/80 mm Hg = 1.00 [95% CI: 0.87, 1.14]; BP 140–159/90-99 mm Hg vs < 130/80 mm Hg = 1.02 [95% CI: 0.93, 1.11]). These findings were consistent across different age groups, treatment for antihypertensive medications, as well as atherosclerotic cardiovascular disease risk.
Conclusion: Among patients with hypertension, uncontrolled BP prior to COVID-19 infection did not appear to be an important risk factor for 30-day mortality or hospitalization.

1. Introduction

Hypertension is one of the most common comorbidities in patients with severe COVID-19 [1]. About half of the patients admitted to the hospital due to COVID-19 as of March 2020 had hypertension [1]. However, hypertension or high blood pressure (BP) as an independent risk factor for severe COVID-19 infection is controversial [2]. A meta-analysis of observational studies suggested that hypertension is an independent predictor for severe COVID-19 outcomes [3]. Another study suggested that high pulse pressure, a marker of arterial stiffness, was associated with higher risk for all-cause mortality in patients hospitalized with COVID-19 [4]. The association between high BP and underlying inflammation has been widely discussed in the previous literature [5]. The pro-inflammatory predisposition of patients with hypertension is proposed as a potential mechanism for severe COVID-19 outcomes [6].

Conversely, studies suggest that hypertension alone is not a risk factor for severe COVID-19 outcomes as the findings may be confounded by older age [7,8]. The association between uncontrolled BP prior to COVID-19 and severity of illness among patients with hypertension would provide additional insights, however, most studies investigated BP levels at the time of hospital admission when COVID-19 may have influenced BP levels. A recent UK study investigating patients with hypertension in general practices showed that uncontrolled BP prior to COVID-19 infection does not carry an increased risk of COVID-19 related complications [9]. Rather, uncontrolled BP was associated with lower risk of death compared with controlled BP, which may be counterintuitive.

The current study evaluated the association between uncontrolled BP and 30-day all-cause hospitalization and/or mortality in patients with hypertension from a large US integrated healthcare system. We also

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Abbreviations

BP = blood pressure
SBP = systolic blood pressure
DBP = diastolic blood pressure
EHRs = electronic health records
KPSC = Kaiser Permanente Southern California
RT-PCR = reverse transcription polymerase chain reaction
ASCVD = atherosclerotic cardiovascular disease
RRs = rate ratios
ORs = odds ratios

evaluated COVID-19 outcomes associated with systolic BP (SBP), diastolic BP (DBP), and pulse pressure levels, separately.

2. Materials and methods

Anonymized data that support the findings of this study may be made available from the investigative team with the following conditions: 1) agreement to collaborate with the study team on all publications, 2) provision of external funding for administrative and investigator time necessary for this collaboration, 3) demonstration that the external investigative team is qualified and has documented evidence of training for human subjects protections, and 4) agreement to abide by the terms outlined in data use agreements between institutions.

2.1. Study setting

We conducted a retrospective observational cohort study of patients with hypertension using data obtained from administrative and electronic health records (EHRs) of Kaiser Permanente Southern California (KPSC), a large US integrated healthcare system. KPSC provides medical services to its members through its own facilities which include 15 hospitals, more than 200 outpatient facilities and a centralized laboratory. Administrative files include demographic, insurance, residence, and membership information. All clinical care and interactions with the healthcare delivery system are captured in comprehensive EHRs including vital signs, laboratory test results, hospitalization, outpatient office visits. Healthcare utilization outside KPSC is also captured through claims. More than 95% of members have a pharmacy benefit and have an incentive to fill their medication within the system. The pharmacy data system at KPSC captures all dispensed prescriptions and pharmacy claims. Death records are identified from hospital discharge records and membership files.

2.2. Study population

We identified patients with hypertension as of March 1, 2020 from the KPSC hypertension registry. Patients were required to have a lab-confirmed, positive reverse transcription polymerase chain reaction (RT-PCR) test for COVID-19 or a diagnosis of COVID-19 between March 1 – September 1, 2020. The index date was the first date of a positive RT-PCR test result or a diagnosis of COVID-19, and the patients were required to be continuously enrolled in the KPSC system for 12 months prior to the index date. We excluded patients without ≥1 outpatient BP measurements 12 months prior to the index date. The study protocol was reviewed and approved by the KPSC institutional review board.

2.3. Blood pressure

We used the most recent outpatient BP measurement during the 12-month period prior to the index date to define BP categories prior to COVID-19 infection. In the primary analysis, SBP <130 and DBP <80 mm Hg (<130/80 mm Hg) was considered as controlled BP according to the 2017 American Heart Association/American College of Cardiology BP guideline and used as a reference group. The remaining BP categories were considered uncontrolled BP, and further classified into: a) SBP 130–139 or DBP 80–89 mm Hg (130–139/80-89 mm Hg); b) SBP 140–159 or DBP 90–99 mm Hg (140–159/90-99 mm Hg); and c) SBP ≥160 or DBP ≥100 mm Hg (≥160/100 mm Hg). In the case of multiple BP measurements on the same day, the lowest BP value was selected to avoid potential white-coat effect.

The secondary analysis investigated SBP (<100, 100–119, 120–139, 140–159, ≥160 mm Hg), DBP (<60, 60–79, 80–89, 90–99, ≥100 mm Hg), and pulse pressure (≤50, 51–60, 61–70, >70 mm Hg), separately, using the most recent outpatient BP measurement during the previous 12 months. Quartiles of SBP, DBP, and pulse pressure were also investigated.

A sensitivity analysis was conducted using the average of all BP measurements during the 12 months prior to the index date.

2.4. Outcomes

The primary outcome of interest was all-cause hospitalization within 30 days of COVID-19 infection and/or all-cause mortality within 30 days of COVID-19 infection. The secondary outcome was all-cause mortality within 30 days of COVID-19 infection.

2.5. Covariates

Covariates included age at index date, sex, race/ethnicity (non-Hispanic White, Asian/Pacific Islander, Non-Hispanic Black, Hispanic, Other/unknown), smoking status, Medicaid insurance, neighborhood income and neighborhood education. History of atherosclerotic cardiovascular disease (ASCVD) was identified using diagnosis codes during the 5 years prior to the index date. For patients without a history of ASCVD, estimated 10-year ASCVD risk was calculated using the Pooled Cohort Equation [10]. Elixhauser comorbidity scores, individual comorbidities (including but not limited to pneumonia, respiratory disease, diabetes, heart failure, asthma, chronic obstructive pulmonary disease, coronary artery disease, and chronic kidney disease), and outpatient medication use (antiplatelet therapy, lipid lowering therapy, insulin, and oral hypoglycemic agents) were determined using diagnosis and pharmacy records during the 12-month period prior to the index date. Antihypertensive medication use and classes (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers; beta-blockers, calcium channel blockers, or diuretics; other classes; no antihypertensive medications) were determined at the index date. A gap in the medication days' supply longer than 20 days from the index date was classified as having no antihypertensive medication. SBP, DBP, and mean arterial pressure (defined as [2 x DBP + SBP]/3) were also used as covariates in some analyses.

2.6. Statistical analyses

We conducted analysis of variance (ANOVA) tests and chi-square tests to compare patient and clinical characteristics among the different BP categories. As a primary analysis, crude and adjusted rate ratios (RRs) and 95% confidence intervals were reported to investigate the associations between BP categories and all-cause hospitalization and/or mortality within 30 days using multivariable Poisson regression models with robust error variance. We first included demographic characteristics as covariates, and then a comprehensive list of pre-selected clinical characteristics including comorbidities and medications [11] was added to the model. For all-cause mortality, logistic regression was performed and odds ratios (ORs) between BP categories and all-cause mortality were reported. In the secondary analysis, in addition to adjustment for other covariates as in the primary analysis, the effect of SBP levels on COVID-19 severity was investigated by further adjusting for DBP as a continuous variable. Similarly, for the effect of DBP levels, SBP as a continuous variable was further adjusted. Mean arterial pressure was further adjusted for the effect of pulse pressure levels.

We conducted *a priori* stratified analyses by age (<65 and ≥65 years), hypertension treatment status (treated and not treated), diabetes (yes and no), history of ASCVD (yes and no), and 10-year ASCVD risk for those who did not have previous ASCVD (<5%, 5–7.4%, 7.5–19.9%, and ≥20%).

All statistical analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute, Cary NC). A $p < 0.05$ was considered statistically significant with no multiplicity adjustment.

3. Results

We included a total of 12,548 patients with hypertension and COVID-19. Among those, 84.6% had a positive RT-PCR test result and 15.4% only had a clinical diagnosis of COVID-19. Mean (SD) age was 59.8 (13.8) years, 47.2% were male, 58.0% Hispanic, 19.9% non-Hispanic White, 9.9% Asian/Pacific Islander, and 9.8% non-Hispanic Black.

Table 1 describes patient demographic and clinical characteristics across BP categories. Mean (SD) time between the most recent outpatient BP measurement and the index date was 128 (96) days. Among the total population, 36.7% of patients had controlled BP (<130/80 mm Hg)

Table 1
Patient characteristics by blood pressure categories.

	Total N = 12,548	<130/80 mm Hg N = 4606 (row percent = 36.7%)	130-139/80–89 mm Hg N = 5437 (43.3%)	140-159/90–99 mm Hg N = 1951 (15.5%)	≥160/100 mm Hg N = 554 (4.4%)
Age in years	59.8±13.8	62.2±13.5	58.9±13.6	58.1±13.9	55.3±14.3
Male sex	5928 (47.2)	2139 (46.4)	2601 (47.8)	920 (47.2)	268 (48.4)
Race/ethnicity					
Non-Hispanic White	2496 (19.9)	1061 (23.0)	1006 (18.5)	341 (17.5)	88 (15.9)
Asian/Pacific Islander	1240 (9.9)	477 (10.4)	543 (10.0)	170 (8.7)	50 (9.0)
Non-Hispanic Black	1233 (9.8)	417 (9.1)	539 (9.9)	204 (10.5)	73 (13.2)
Hispanic	7282 (58.0)	2564 (55.7)	3209 (59.0)	1189 (60.9)	320 (57.8)
Other/Unknown	297 (2.4)	87 (1.9)	140 (2.6)	47 (2.4)	23 (4.2)
Body Mass Index (kg/m^2)	32.5 ±7.2	31.8 ±7.2	32.9 ±7.1	33.1 ±7.3	33.5 ±7.5
Smoking status					
Current	378 (3.0)	129 (2.8)	165 (3.0)	57 (2.9)	27 (4.9)
Former	3588 (28.6)	1442 (31.3)	1511 (27.8)	490 (25.1)	145 (26.2)
Never/Missing*	8582 (68.4)	3035 (65.9)	3761 (69.2)	1404 (72.0)	382 (68.9)
Medicaid indicator	1258 (10.1)	513 (11.2)	504 (9.3)	187 (9.6)	54 (9.8)
Neighborhood Income†					
$0-49k	3275 (26.1)	1178 (25.6)	1411 (26.0)	528 (27.1)	158 (28.5)
$50-79k	5354 (42.7)	1941 (42.1)	2338 (43.0)	827 (42.4)	248 (44.8)
$80-99k	2178 (17.4)	805 (17.5)	957 (17.6)	329 (16.9)	87 (15.7)
≥$100k	1728 (13.8)	677 (14.7)	725 (13.3)	267 (13.7)	59 (10.6)
Neighborhood Education (% of ≥High School Graduate)†					
0–50%	873 (7.0)	302 (6.6)	365 (6.7)	166 (8.5)	40 (7.2)
51–75%	4670 (37.2)	1671 (36.3)	2072 (38.1)	719 (36.9)	208 (37.5)
76–100%	6994 (55.7)	2628 (57.1)	2995 (55.1)	1066 (54.6)	305 (55.1)
History of ASCVD	1020 (8.1)	470 (10.2)	341 (6.3)	151 (7.7)	58 (10.5)
10-year ASCVD risk‡					
<5%	3265 (33.8)	1258 (35.8)	1463 (34.1)	440 (29.7)	104 (27.2)
5–7.4%	1310 (13.5)	469 (13.3)	577 (13.4)	206 (13.9)	58 (15.2)
7.5–19.9%	3294 (34.1)	1188 (33.8)	1480 (34.5)	510 (34.4)	116 (30.4)
≥20%	1805 (18.7)	603 (17.1)	771 (18.0)	327 (22.0)	104 (27.2)
Elixhauser comorbidity score					
0	596 (4.7)	175 (3.8)	296 (5.4)	101 (5.2)	24 (4.3)
1-3	7535 (60.0)	2473 (53.7)	3483 (64.1)	1235 (63.3)	344 (62.1)
4+	4417 (35.2)	1958 (42.5)	1658 (30.5)	615 (31.5)	186 (33.6)
Pneumonia	1862 (14.8)	768 (16.7)	716 (13.2)	286 (14.7)	92 (16.6)
Respiratory disease	403 (3.2)	180 (3.9)	148 (2.7)	55 (2.8)	20 (3.6)
Diabetes	4885 (38.9)	1965 (42.7)	1992 (36.6)	723 (37.1)	205 (37.0)
Heart failure	358 (2.9)	177 (3.8)	113 (2.1)	52 (2.7)	16 (2.9)
Asthma	1161 (9.3)	461 (10.0)	481 (8.8)	174 (8.9)	45 (8.1)
Chronic obstructive pulmonary disease	457 (3.6)	228 (5.0)	160 (2.9)	59 (3.0)	10 (1.8)
Coronary artery disease	894 (7.1)	445 (9.7)	293 (5.4)	120 (6.2)	36 (6.5)
Chronic kidney disease	877 (7.0)	411 (8.9)	298 (5.5)	130 (6.7)	38 (6.9)
Metastatic cancer	134 (1.1)	68 (1.5)	46 (0.8)	16 (0.8)	4 (0.7)
Antihypertensive Medications					
ACEI	4236 (33.8)	1726 (37.5)	1803 (33.2)	568 (29.1)	139 (25.1)
ARB	2400 (19.1)	838 (18.2)	1040 (19.1)	405 (20.8)	117 (21.1)
BB or CCB or Diuretics	2450 (19.5)	903 (19.6)	1098 (20.2)	355 (18.2)	94 (17.0)
Other antihypertensive meds	140 (1.1)	60 (1.3)	56 (1.0)	16 (0.8)	8 (1.4)
No antihypertensive medications	3322 (26.5)	1079 (23.4)	1440 (26.5)	607 (31.1)	196 (35.4)
Outpatient Medications					
Antiplatelet	1014 (8.1)	456 (9.9)	391 (7.2)	133 (6.8)	34 (6.1)
Lipid lowering	7067 (56.3)	2866 (62.2)	2981 (54.8)	990 (50.7)	230 (41.5)
Insulin	1773 (14.1)	711 (15.4)	707 (13.0)	279 (14.3)	76 (13.7)
Oral hypoglycemics	4120 (32.8)	1616 (35.1)	1749 (32.2)	602 (30.9)	153 (27.6)

Mean ± SD or N (column percent) are reported. Abbreviations: ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; ASCVD = atherosclerotic cardiovascular disease; BB = beta-blockers; CCB = calcium channel blockers. *2% missing for smoking status. †0.1% missing for Neighborhood Income and neighborhood education. ‡Only among those without history of ASCVD, with age between 40 and 75 years, and had available information to estimate 10-year ASCVD risk (N = 9674).

prior to COVID-19 infection while 43.3% had BP 130–139/80-89 mm Hg, 15.5% had BP 140–159/90-99 mm Hg, and 4.4% had BP ≥ 160/100 mm Hg. Patients with BP ≥ 160/100 mm Hg were younger, had a higher percentage of non-Hispanic Black, and a higher estimated 10-year ASCVD risk and a higher percent of not receiving any antihypertensive medications compared with lower BP categories.

In this cohort, 20.9% of patients were hospitalized within 30 days of COVID-19 infection, 4.1% were admitted to intensive care units, and all-cause 30-day mortality alone was 4.6% (Supplement Table S1). Table 2 shows comparison of all-cause hospitalization and/or mortality outcomes among patients with different BP levels. Patients with controlled BP had a higher risk of hospitalization or death compared with other BP levels prior to any covariate adjustment. However, these were not statistically significant after covariate adjustment (RR for BP ≥ 160/100 mm Hg vs < 130/80 mm Hg = 1.00 [95% CI 0.87, 1.14]). Findings were consistent for all-cause mortality (OR for BP ≥ 160/100 mm Hg vs < 130/80 mm Hg = 1.30 [95% CI 0.82, 2.08]). Sensitivity analyses using the average of all BP measurements in the 12 months prior to the index date (median [interquartile ranges] BP measurements = 3 [1,5]) demonstrated similar results (Supplement Table S2).

Table 3 shows all-cause hospitalization or mortality associated with SBP, DBP, and pulse pressure, separately. A higher SBP (SBP ≥160 mm Hg vs 100–119 mm Hg) was associated with a higher risk of hospitalization and/or mortality after adjusting for DBP (RR = 1.65 [95% CI 1.36, 2.00]), however, a higher SBP was not statistically significantly associated with outcomes after adjusting for other confounders (RR = 1.16 [95% CI 0.94, 1.43]). A higher DBP (DBP ≥100 mm Hg vs < 60 mm Hg) was associated with a lower risk of hospitalization and/or mortality after adjusting for SBP (RR = 0.34 [95% CI 0.25, 0.47]), but it was no longer statistically significant after adjusting for other confounders (RR = 0.82 [95% CI 0.63, 1.07]). A higher pulse pressure (pulse pressure >70 mm Hg vs ≤ 50 mm Hg) was associated with a higher risk of hospitalization and/or mortality after adjusting for mean arterial pressure (RR = 1.52 [95% CI 1.38, 1.67]), however, it was not statistically significant after adjusting for all covariates (RR = 1.04 [95% CI 0.96, 1.13]). Analyses using quartiles of SBP, DBP, and pulse pressure showed similar results (Supplement Table S3).

Interaction tests examining whether the outcomes associated with BP categories differed based on patient age, antihypertensive medication use, diabetes, history of ASCVD, and 10-year ASCVD risk were not statistically significant ($p > 0.05$). Because of existing clinical interest, we still performed *a priori* specified stratified analyses. Uncontrolled BP was not associated with a higher risk of hospitalization and/or mortality after COVID-19 infection across all subgroups examined (Table 4).

Although there was no statistically significant association between uncontrolled BP and hospitalization and/or mortality, having healthcare encounters with a hypertension diagnosis, and no antihypertensive medication use within 12 months prior to the index date were associated with a higher risk of hospitalization and/or mortality (Supplemental Table S4). Also, cardiovascular comorbidities such as coronary artery disease and chronic kidney disease were associated with increased hospitalization or mortality. Other sociodemographic and clinical characteristics associated with hospitalization and/or mortality outcomes included older age (40–64, 65–74, ≥85 years vs 18–39 years), male sex (vs female), Asian/Pacific Islander (vs non-Hispanic White), a higher body mass index ≥40 (vs < 25), a higher Elixhauser comorbidity score (≥4 vs 0), and comorbidities including pneumonia, respiratory lung disease, metastatic cancer, and diabetes.

Table 2
Rate Ratios (RR) or Odds Ratios (OR) of 30-day All-Cause Hospitalization and/or Mortality Associated with Uncontrolled Blood Pressure among Patients with Hypertension and COVID-19 (Total N = 12,548).

BP Categories	N (%)	Crude RR (95% CI)	Adjusted RR (95% CI)[a]	Adjusted RR (95% CI)[b]
Hospitalization or all-cause mortality within 30 days of COVID-19 Infection				
<130/80 mm Hg (N = 4606)	1133 (24.6%)	Reference	Reference	Reference
130-139/80–89 mm Hg (N = 5437)	1045 (19.2%)	0.78 (0.72, 0.84)	0.87 (0.81, 0.94)	0.99 (0.93, 1.06)
140-159/90–99 mm Hg (N = 1951)	395 (20.2%)	0.82 (0.74, 0.91)	0.94 (0.85, 1.03)	1.02 (0.93, 1.11)
≥160/100 mm Hg (N = 554)	114 (20.6%)	0.83 (0.69, 0.98)	1.02 (0.86, 1.20)	1.00 (0.87, 1.14)
BP Categories	**N (%)**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)[a]**	**Adjusted OR (95% CI)[b]**
All-cause mortality within 30 days of COVID-19 Infection				
<130/80 mm Hg (N = 4606)	265 (5.8%)	Reference	Reference	Reference
130-139/80–89 mm Hg (N = 5437)	204 (3.8%)	0.64 (0.53, 0.77)	0.81 (0.66, 0.98)	1.00 (0.81, 1.24)
140-159/90–99 mm Hg (N = 1951)	75 (3.8%)	0.65 (0.50, 0.85)	0.84 (0.64, 1.11)	0.93 (0.69, 1.25)
≥160/100 mm Hg (N = 554)	27 (4.9%)	0.84 (0.56, 1.26)	1.34 (0.87, 2.05)	1.30 (0.82, 2.08)

Abbreviations: BP = blood pressure; CI = confidence interval; OR = odds ratio; RR = rate ratio.
[a] Adjusted for age, sex, race/ethnicity, antihypertensive medication.
[b] Adjusted for demographic, socioeconomic characteristics, pre-selected comorbidities, and medications.

Table 3
Rate ratios (RR) of 30-day all-cause hospitalization or mortality associated with systolic and diastolic blood pressure, and pulse pressure among patients with hypertension and COVID-19.

BP levels	RR[a]	RR[b]	RR[c]	RR[d]
Systolic BP				
<100 mm Hg (N = 278)	1.37 (1.15, 1.64)	1.01 (0.84, 1.20)	1.04 (0.88, 1.24)	1.03 (0.87, 1.22)
100–119 mm Hg (N = 2210)	Reference	Reference	Reference	Reference
120–139 mm Hg (N = 7883)	0.79 (0.73, 0.86)	0.94 (0.86, 1.02)	0.91 (0.84, 0.99)	1.01 (0.86, 1.18)
140–159 mm Hg (N = 1821)	0.79 (0.71, 0.89)	1.13 (1.00, 1.28)	1.01 (0.90, 1.14)	1.00 (0.86, 1.16)
≥160 mm Hg (N = 356)	1.03 (0.85, 1.25)	1.65 (1.36, 2.00)	1.38 (1.14, 1.68)	1.16 (0.94, 1.43)
Diastolic BP				
<60 mm Hg (N = 1491)	Reference	Reference	Reference	Reference
60–79 mm Hg (N = 6965)	0.59 (0.55, 0.64)	0.58 (0.54, 0.63)	0.80 (0.73, 0.87)	0.97 (0.90, 1.04)
80–89 mm Hg (N = 3074)	0.44 (0.39, 0.49)	0.43 (0.38, 0.48)	0.71 (0.63, 0.80)	0.92 (0.83, 1.02)
90–99 mm Hg (N = 743)	0.44 (0.37, 0.53)	0.43 (0.35, 0.51)	0.76 (0.63, 0.92)	0.95 (0.81, 1.12)
≥100 mm Hg (N = 275)	0.36 (0.27, 0.50)	0.34 (0.25, 0.47)	0.69 (0.50, 0.95)	0.82 (0.63, 1.07)
Pulse Pressure				
≤50 mm Hg (N = 4562)	Reference	Reference	Reference	Reference
51–60 mm Hg (N = 3745)	1.04 (0.95, 1.14)	1.07 (0.98, 1.17)	0.98 (0.90, 1.07)	1.01 (0.93, 1.09)
61–70 mm Hg (N = 2482)	1.35 (1.23, 1.48)	1.33 (1.22, 1.46)	1.09 (1.00, 1.20)	1.07 (0.99, 1.16)
>70 mm Hg (N = 1759)	1.58 (1.44, 1.74)	1.52 (1.38, 1.67)	1.16 (1.05, 1.28)	1.04 (0.96, 1.13)

Abbreviations: BP = blood pressure; RR = rate ratio.
[a] Crude RR.
[b] Adjusted for continuous DBP for SBP level variable; adjust for continuous SBP for DBP level variable; adjust for mean arterial pressure for Pulse Pressure level variable.
[c] Adjusted for age, sex, race/ethnicity, DBP (or SBP or mean arterial pressure), antihypertensive medication.
[d] Adjusted for demographic, socioeconomic characteristics, DBP (or SBP or mean arterial pressure), pre-selected comorbidities, and medications.

Table 4
Rate Ratios of 30-day All-Cause Hospitalization or Mortality Associated with Uncontrolled Blood Pressure Stratified by Treatment Status and Atherosclerotic Cardiovascular Disease (ASCVD) risk.

	<130/80 mm Hg	130-139/ 80–89 mm Hg	140-159/ 90–99 mm Hg	≥160/100 mm Hg
Age				
<65 years (N = 8123)	Reference	1.05 (0.93, 1.17)	1.05 (0.91, 1.22)	1.00 (0.81, 1.23)
≥65 years (N = 4425)	Reference	0.96 (0.89, 1.03)	0.98 (0.88, 1.08)	0.92 (0.77, 1.11)
Antihypertensive Medication Use				
Yes (N = 9226)	Reference	0.99 (0.92, 1.07)	1.01 (0.92, 1.12)	1.00 (0.85, 1.18)
No (N = 3322)	Reference	1.01 (0.89, 1.16)	1.02 (0.86, 1.21)	0.96 (0.72, 1.26)
Diabetes				
Yes (N = 4885)	Reference	1.00 (0.92, 1.08)	1.03 (0.93, 1.15)	1.06 (0.90, 1.24)
No (N = 7663)	Reference	0.97 (0.88, 1.07)	0.98 (0.85, 1.12)	0.88 (0.69, 1.14)
ASCVD History				
Yes (N = 1020)	Reference	1.03 (0.91, 1.17)	1.00 (0.86, 1.17)	1.05 (0.83, 1.33)
No (N = 11,528)	Reference	0.99 (0.92, 1.07)	1.02 (0.93, 1.13)	0.97 (0.82, 1.15)
10-year ASCVD Risk[a]				
<5% (N = 3265)	Reference	0.93 (0.75, 1.16)	1.11 (0.84, 1.47)	0.75 (0.41, 1.38)
5–7.4% (N = 1310)	Reference	1.14 (0.84, 1.54)	1.40 (0.93, 2.09)	1.29 (0.61, 2.74)
7.5–19.9% (N = 3294)	Reference	0.90 (0.78, 1.04)	0.82 (0.66, 1.02)	0.76 (0.51, 1.15)
≥20% (N = 1805)	Reference	0.91 (0.81, 1.03)	0.82 (0.69, 0.98)	1.07 (0.83, 1.38)

Abbreviation: ASCVD = atherosclerotic cardiovascular disease.
[a] Only among those without a history of ASCVD, with age between 40 and 75 years, and had available information to estimate 10-year ASCVD risk (N = 9674).

4. Discussion

Our study found no evidence of association between uncontrolled BP prior to COVID-19 infection and all-cause hospitalization and/or mortality for patients with hypertension. These findings were consistent for different age groups, for those who were treated and untreated with antihypertensive medications, for those with a history of ASCVD or different 10-year ASCVD risk. We observed that older age, body mass index, diabetes, and cardiovascular comorbidities such as coronary artery disease and chronic kidney disease were associated with hospitalization and/or mortality in patients with hypertension.

Early in the COVID-19 pandemic, there were concerns regarding a higher proportion of hypertension patients among those admitted to the hospital due to COVID-19. While frequently used antihypertensive medications such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers were proposed as a potential mechanism of harm, various studies confirmed that these medications are not risk factors for severe COVID-19 outcomes [11–15]. However, whether high BP is an independent risk factor for severe COVID-19 outcome is controversial. Several meta-analyses suggest that hypertension is associated with a two-fold higher risk of COVID-19 severity [3,16]. On the other hand, other studies suggest that hypertension alone is not an independent risk factor for COVID-19 mortality [7].

Our study aimed to determine if uncontrolled BP in patients with hypertension is a risk factor for all-cause hospitalization and/or mortality. Data regarding the effect of high BP among patients with hypertension is currently limited. An observational study from China investigating 803 hospitalized patients with COVID-19 and hypertension showed that high in-hospital SBP and pulse pressure were associated with heart failure development, but not mortality [17]. Another study from Spain evaluating 12,170 hypertensive patients hospitalized due to COVID-19 concluded that high pulse pressure and SBP <120 mm Hg were associated with a higher risk for all-cause mortality [4]. However, these studies evaluated BP at the time of hospital admission or during hospitalization where COVID-19 may have already influenced BP levels, therefore, these studies do not answer whether prior uncontrolled BP in hypertension increases the risk of serious COVID-19 cases. Finally, a recent UK study evaluated 45,418 patients with hypertension in general practices and showed poorly controlled BP prior to COVID-19 infection was associated with a “lower” risk of COVID-19 related complications [9].

Similar to the UK study, our study investigated patients with hypertension and outpatient BP measurements prior to COVID-19 infection. However, unlike the UK study, our study focused on patients with a positive RT-PCR COVID-19 test or diagnosis of COVID-19, instead of all patients with hypertension tested for COVID-19. This reduced potential biases due to testing differences (i.e. patients who were simply tested by RT-PCR may be very different from patients who tested positive for COVID-19 by RT-PCR). In addition, our study population was younger, racially/ethnically diverse, more obese, but had better BP control, and had a lower percentage of chronic kidney disease than the population included in the UK study. These population differences may have led to distinct study findings. Although crude RRs or ORs from our study showed associations between uncontrolled BP and hospitalization and/or mortality, uncontrolled BP was not independently associated with hospitalization and/or mortality after adjusting for demographics and clinical characteristics.

Consistent with previous literature, our study found that older age was the most significant risk factor for hospitalization and/or mortality. In addition to respiratory disease, a higher number of comorbidities, severe obesity, diabetes, chronic kidney disease, and coronary artery disease were significant independent risk factors for all-cause hospitalization and/or mortality [18–20]. Moreover, having health care encounters with a hypertension diagnosis within 12 months prior to the index date was associated with outcomes, which may be a proxy for severity of hypertension. Worse clinical outcomes were observed in the group exposed to no antihypertensive medication. This may be due to unmeasured poor health-related behaviors of nonadherent patients rather than related to uncontrolled BP.

This study has several strengths and limitations. This is the largest cohort study investigating the relationship between BP control and hospitalization/mortality among patients with hypertension and COVID-19 infection in the US. Using comprehensive EHRs of patients with hypertension, our study findings provide insights regarding the role of high BP in patients infected with COVID-19. However, our study cohort had a relatively small proportion of patients with BP ≥ 160/100 mm Hg. Distribution of BP levels may have impacted the study results. In addition, BP levels were determined based on the most recent outpatient BP measurements prior to COVID-19 infection. Although this is a proxy for BP control, the sensitivity analysis results using the average BP levels during the 12 months prior to index produced similar findings. Moreover, antihypertensive medication use was measured at index using pharmacy dispense records in our system, therefore, medication use can be potentially misclassified. BP levels can also be affected by medication use, and the timing of BP and medication use were not investigated. Because covariates were pre-selected based on prior publication or clinical interest, there is a possibility of unmeasured confounders. Our study outcome was all-cause hospitalization and mortality within 30 days of COVID-19 infection. Although we were not able to confirm causes of death or hospitalization as COVID-19 for all cases, over 99% hospitalization records had a primary or secondary diagnosis of COVID-19, and only 63 (2%) patients died without hospitalization.

5. Conclusions

The current study found no association of uncontrolled BP prior to

COVID-19 infection with 30-day all-cause hospitalizations and/or mortality among patients with hypertension. While BP control is an important chronic treatment goal, its role in an acute viral illness such as COVID-19 is yet to be determined.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2021.200117.

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Declarations of interest

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