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

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\textbf{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 140–159/90–99 mm Hg vs ≤130/80 mm Hg = 1.00 [95% CI: 0.87, 1.14]; 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 atherothrombotic 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.

\section{1. Introduction}

Hypertension is one of the most common comorbidities in patients with severe COVID-19 \cite{1}. About half of the patients admitted to the hospital due to COVID-19 as of March 2020 had hypertension \cite{1}. However, hypertension or high blood pressure (BP) as an independent risk factor for severe COVID-19 infection is controversial \cite{2}. A meta-analysis of observational studies suggested that hypertension is an independent predictor for severe COVID-19 outcomes \cite{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 \cite{4}. The association between high BP and underlying inflammation has been widely discussed in the previous literature \cite{5}. The pro-inflammatory predisposition of patients with hypertension is proposed as a potential mechanism for severe COVID-19 outcomes \cite{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 \cite{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 \cite{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 (100–109, 120–139, 140–159, >160 mm Hg), DBP (60–69, 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%, 7.5–9.9%, and ≥10%).

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.

### Table 1

Patient characteristics by blood pressure categories.

|                  | <130/80 mm Hg | 130-139/80-89 mm Hg | 140-159/90-99 mm Hg | ≥160/100 mm Hg |
|------------------|--------------|-----------------|-------------------|--------------|
| Age in years     |              |                 |                   |              |
| Total N = 12,548 | N = 4606      | N = 5437        | N = 1951          | N = 554       |
| Male sex         | 5928±13.8    | 2319±46.4       | 920±47.8          | 268±48.4     |
| Female sex       | 5928±13.8    | 2319±46.4       | 920±47.8          | 268±48.4     |
| Race/ethnicity   |              |                 |                   |              |
| Non-Hispanic White | 2496±19.9   | 1061±23.0       | 341±17.5          | 88±15.9      |
| Asian/Pacific Islander | 1240±9.9 | 477±10.4        | 170±8.7           | 50±9.0       |
| Non-Hispanic Black | 1233±9.8   | 417±9.1         | 204±10.5          | 73±13.2      |
| Hispanic         | 7282±58.0    | 2564±55.7       | 1189±60.9         | 320±57.8     |
| Other/Unknown    | 297±12.4     | 87±1.9          | 47±2.4            | 23±4.2       |
| Body Mass Index (kg/m²) | 32.5±7.2 | 31.8±7.2        | 33.1±7.3          | 33.5±7.5     |
| Smoking status   |              |                 |                   |              |
| Current          | 378±3.0      | 129±2.8         | 57±2.9            | 27±4.9       |
| Former           | 3588±28.6    | 1442±33.1       | 490±25.1          | 145±26.2     |
| Never/Missing†   | 8582±68.4    | 3035±65.9       | 1040±72.0         | 302±68.9     |
| Medication indicator | 1258±10.1 | 513±11.2        | 187±9.6           | 54±9.8       |
| Neighborhood Income‡ | 3275±26.1 | 1178±25.6       | 528±27.1          | 158±28.5     |
| $30-49k          | 3534±42.7    | 1941±42.1       | 827±42.4          | 248±44.8     |
| $50-79k          | 2178±17.4    | 805±17.6        | 326±16.9          | 87±15.7      |
| <$100k           | 1728±13.8    | 677±14.7        | 267±13.7          | 59±10.6      |
| Neighborhood Education (% of ≥High School Graduate)† | 873 (7.0) | 302 (6.6) | 166 (8.5) | 40 (7.2) |
| 0-50%            | 4670 (37.2)  | 1671 (36.3)     | 719 (36.9)        | 208 (37.5)   |
| 51-75%           | 6994 (55.7)  | 2628 (57.1)     | 1066 (54.6)       | 305 (55.1)   |
| 76-100%          | 1020 (8.1)   | 470 (10.2)      | 151 (7.7)         | 58 (10.5)    |
| 10-year ASCVD risk‡ |              |                 |                   |              |
| ≥5%              | 3265 (33.8)  | 1258 (35.8)     | 440 (29.7)        | 104 (27.2)   |
| 5.7-4%           | 1310 (13.5)  | 469 (13.3)      | 206 (13.9)        | 58 (15.2)    |
| 7.5-19.9%        | 3294 (34.8)  | 1188 (33.8)     | 510 (34.8)        | 116 (30.4)   |
| ≥20%             | 1805 (17.8)  | 603 (17.1)      | 327 (22.0)        | 104 (27.2)   |
| Elixhauser comorbidity score | 0          | 596 (4.7)       | 296 (5.4)         | 101 (5.2)    |
| 1-3              | 7535 (60.0)  | 2473 (32.7)     | 1235 (36.3)       | 344 (62.1)   |
| 4+               | 4417 (37.2)  | 1958 (42.5)     | 615 (31.5)        | 186 (33.6)   |
| Pneumonia        | 1862 (14.8)  | 768 (16.7)      | 286 (14.7)        | 92 (16.6)    |
| Respiratory disease | 403 (3.2) | 180 (3.9)       | 55 (2.8)          | 20 (3.6)     |
| Diabetes         | 4885 (38.9)  | 1602 (42.7)     | 723 (37.1)        | 205 (37.0)   |
| Heart failure    | 358 (2.9)    | 177 (3.8)       | 52 (2.7)          | 16 (2.9)     |
| Asthma           | 1161 (9.3)   | 461 (10.0)      | 174 (8.9)         | 45 (8.1)     |
| Chronic obstructive pulmonary disease | 457 (3.6) | 228 (5.0)       | 59 (3.0)          | 10 (1.8)     |
| Coronary artery disease | 894 (7.1) | 445 (9.7)       | 120 (6.2)         | 36 (6.5)     |
| Chronic kidney disease | 877 (7.0) | 411 (8.9)       | 130 (6.7)         | 38 (6.9)     |
| Metastatic cancer | 134 (1.1)   | 68 (1.5)        | 16 (0.8)          | 4 (0.7)      |

### 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).
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 = 1.04 [95% CI 1.00, 1.09]).

### Table 2

| BP Categories | N (%) | Crude RR (95% CI) | Adjusted RR (95% CI) | Adjusted RR (95% CI) |
|---------------|-------|------------------|---------------------|---------------------|
| <130/80 mm Hg (N = 4066) | 1133 | 1.00 (Reference) | Reference | Reference |
| 130–159/80–89 mm Hg (N = 5437) | 1045 | 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 | 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 | 0.83 (0.69, 0.98) | 1.02 (0.86, 1.20) | 1.00 (0.87, 1.14) |

### Table 3

| BP levels | RR a | RR b | RR c | RR d |
|-----------|------|------|------|------|
| <100 mm Hg (N = 1491) | 1.37 (1.15, 1.64) | 1.04 (0.88, 1.24) | 1.03 (0.87, 1.22) |
| 100–119 mm Hg (N = 2210) | 0.79 (0.73, 0.86) | 0.91 (0.86, 0.96) | 1.01 (0.86, 1.25) |
| 120–139 mm Hg (N = 7883) | 0.89 (0.81, 1.02) | 1.13 (1.00, 1.28) | 1.14 (1.00, 1.27) |
| 140–159 mm Hg (N = 1821) | 0.89 (0.81, 1.02) | 1.30 (1.13, 1.48) | 1.38 (1.14, 1.61) |
| ≥160 mm Hg (N = 356) | 1.25 (1.00, 1.52) | 1.65 (1.36, 2.00) | 1.68 (1.34, 2.08) |

### Table 4

| BP Categories | N (%) | Crude OR (95% CI) | Adjusted OR (95% CI) | Adjusted OR (95% CI) |
|---------------|-------|-------------------|---------------------|---------------------|
| All-cause mortality within 30 days of COVID-19 Infection (N = 4066) | 265 | 1.00 (Reference) | Reference | Reference |
| 130–159/80–89 mm Hg (N = 5437) | 204 | 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 | 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 | 0.84 (0.56, 1.26) | 1.34 (0.87, 2.05) | 1.30 (0.82, 2.00) |

Abbreviations: BP = blood pressure; CI = confidence interval; OR = odds ratio; RR = rate ratio.

a Adjusted for age, sex, race/ethnicity, and comorbidities.
b Adjusted for age, sex, race/ethnicity, DBP, SBP, SBP category, and comorbidities.
c Adjusted for age, sex, race/ethnicity, DBP, SBP, SBP category, and antihypertensive medication.
d Adjusted for age, sex, race/ethnicity, DBP, SBP, SBP category, precarism, and comorbidities.

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, 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).

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).
other hand, other studies suggest that hypertension alone is not an in
controvertial. Several meta-analyses suggest that hypertension is asso
ciated with heart failure development, but not mortality [17]. Another
antihypertensive medications, for those with a history of ASCVD or
prior to COVID-19 infection and all-cause hospitalization and/or mor
4. Discussion

Our study found no evidence of association between uncontrolled BP
prior to COVID-19 infection and all-cause hospitalization and/or mor
tality 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 ar
dtery disease and chronic kidney disease were associated with hospital
ization 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 medica
tions 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 asso
ciated 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 in
dependent 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 mor
tality. Data regarding the effect of high BP among patients with hyper
tension is currently limited. An observational study from China
investigating 803 hospitalized patients with COVID-19 and hyperten
sion showed that high in-hospital SBP and pulse pressure were associ
ated 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 gen
eral practices and showed poorly controlled BP prior to COVID-19
infection was associated with a “lower” risk of COVID-19 related com
plications [9].

Similar to the UK study, our study investigated patients with hy
pertension and outpatient BP measurements prior to COVID-19 infec
tion. 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
diases 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 RR 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 hospital
ization and/or mortality [18–20]. Moreover, having health care en
ounters 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. More
over, antihypertensive medication use was measured at index using
RT-PCR may be very different from patients who tested positive
for COVID-19 by RT-PCR. In addition, our study population was younger,
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BP measurements prior to COVID-19 infection. Although this is a proxy
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during the 12 months prior to index produced similar findings. More
over, 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

| Age            | <65 years (N = 8123) | Reference | 1.05 (0.93, 1.05 (0.91, 1.00 (0.81, 1.23) |
|               | 86-95 years (N = 3265) | Reference | 1.17 (1.22) |
|               | ≥90-99 years (N = 11,528) | Reference | 0.96 (0.89, 0.98 (0.88, 0.92 (0.77, 4425) |
|               | ≥100-100 years (N = 1020) | Reference | 1.03 (1.08) |
| Antihypertensive Medication Use | Yes (N = 9226) | Reference | 0.99 (0.92, 1.01 (0.92, 1.00 (0.85, 1.07) |
|               | No (N = 3322) | Reference | 1.01 (0.89, 1.02 (0.86, 0.96 (0.72, 1.16) |
|               | No (N = 7663) | Reference | 0.97 (0.88, 0.98 (0.85, 0.88 (0.69, 1.07) |
| Diabetes       | Yes (N = 4885) | Reference | 1.00 (0.92, 1.03 (0.93, 1.06 (0.90, 1.08) |
|               | No (N = 7663) | Reference | 0.97 (0.88, 0.98 (0.85, 0.88 (0.69, 1.07) |
| ASCVD History  | Yes (N = 1020) | Reference | 1.03 (0.91, 1.06 (0.86, 1.05 (0.83, 1.17) |
|               | No (N = 11,528) | Reference | 0.99 (0.92, 1.02 (0.93, 0.97 (0.82, 1.07) |
| 10-year ASCVD Risk | <5% (N = 3265) | Reference | 0.93 (0.75, 1.11 (0.84, 0.75 (0.41, 1.16) |
|               | 5-7.4% (N = 11,414) | Reference | 0.97 (0.84, 1.14 (0.90, 1.29 (0.61, 0.15) |
|               | 7.5-19.9% (N = 3194) | Reference | 0.90 (0.78, 0.82 (0.66, 0.76 (0.51, 1.04) |
|               | ≥20% (N = 1805) | Reference | 0.91 (0.81, 0.82 (0.69, 1.07 (0.83, 1.03) |

Abbreviation: ASCVD = atherosclerotic cardiovascular disease.

* 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).
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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