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Severe inpatient hypertension prevalence and blood pressure response to antihypertensive treatment

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Abstract

Severe hypertension (HTN) that develops during hospitalization is more common than admission for HTN; however, it is poorly studied, and treatment guidelines are lacking. Our goal is to characterize hospitalized patients who develop severe HTN and assess blood pressure (BP) response to treatment. This is a multi-hospital retrospective cohort study of adults admitted for reasons other than HTN who developed severe HTN. The authors defined severe inpatient HTN as the first documented BP elevation (systolic BP > 180 or diastolic BP > 110) at least 1 hour after admission. Treatment was defined as receiving antihypertensives (intravenous [IV] or oral) within 6h of BP elevation. As a measure of possible overtreatment, the authors studied the association between treatment and time to mean arterial pressure (MAP) drop $\geq$ 30% using the Cox proportional hazards model. Among 224 265 hospitalized adults, 10% developed severe HTN of which 40% were treated. Compared to patients who did not develop severe HTN, those who did were older, more commonly women and black, and had more comorbidities. Incident MAP drop $\geq$ 30% among treated and untreated patients with severe HTN was 2.2 versus 5.7/1000 person-hours. After adjustment, treated versus. untreated patients had lower rates of MAP drop $\geq$ 30% (hazard rate [HR]: 0.9 [0.8, 0.99]). However, those receiving only IV treatment versus untreated had greater rates of MAP drop $\geq$ 30% (1.4 [1.2, 1.7]). Overall, the authors found that clinically significant MAP drop is observed among inpatients with severe HTN irrespective of treatment, with greater rates observed among patients treated only with IV antihypertensives. Further research is needed to phenotype inpatients with severe HTN.

KEYWORDS
antihypertensive therapy, blood pressure response, electronic health records, hypertension, inpatient

1 | INTRODUCTION

Hypertension (HTN) is common in hospitalized patients with prevalence rates up to 72%.[1] In patients who are admitted for severe HTN (systolic/diastolic blood pressure [SBP/DBP] > 180/110 mm Hg) with acute end organ damage, that is, hypertensive emergency, immediate intravenous (IV) pharmacotherapy under intensive care monitoring is recommended to limit progressive injury.[2] However, far more common is incident severe HTN in already hospitalized patients occurring during an admission unrelated to HTN.[3–5] Increased blood pressure (BP) in ambulatory patients is associated with increased risk of cardiovascular disease (CVD) related outcomes including stroke, myocardial infarction and coronary artery disease increases, but treatment of severe inpatient HTN in the absence of acute target organ injury is currently not directed by guidelines.[6,7] Additionally, recent studies have found that treatment of severe inpatient HTN resulted in greater BP drops, and higher rates of acute kidney injury and myocardial injury.[5,8] However, these studies used different study populations (Rastogi and coworkers excluded cardiac admissions), used a wide range of blood pressure (BP) thresholds, and did not account for patient level factors (eg, pain, anxiety).[1,5,8]

Because severe HTN that develops during hospitalization is poorly studied and management remains arbitrary, understanding the actual real-world practice of identifying and treating severe HTN is essential. To address this evidence gap and limitations of previous study, we conducted a retrospective cohort study of adults admitted to five teaching hospitals in Connecticut. Our goal was to leverage data from this large healthcare system to determine prevalence of severe inpatient HTN, to characterize how severe HTN is managed, and to understand how often antihypertensive treatment leads to excessive BP reduction (Figure 1).

2 | METHODS

2.1 | Study population

We included adult patients admitted to one of the five Yale New Haven Health System (YNHHS) Network hospitals between January 1, 2016 and March 31, 2020 with a length of stay ≥2 days and ≤30 days. We excluded patients hospitalized with hypertensive emergency (based on International Classification of Diseases-10 codes [ICD-10]: I16.0, I16.1, I16.9), or to the maternity ward, intensive care unit, or research unit. Patients opting out of research studies were excluded (< 1% of YNNHS). For patients with multiple admissions during the study period, we only included data from their first admission. Patients who received vasopressors 0–6 hours before developing severe HTN were excluded in analysis of antihypertensive therapy (Figure 2). We used a longitudinal dataset with time varying BP measurements and antihypertensive medication administration. This study was approved by the Yale Human Investigation Committee (HIC # 2000028801). Electronic health record data (EHR) was collected from the YNNHS data warehouse (EPIC, Verona WI, USA).

2.2 | Severe inpatient HTN definition

Severe inpatient HTN was defined as the first documented severe BP elevation (SBP > 180 or DBP > 110 mm Hg) reported after admission to the floor and did not include BPs captured in the emergency department. To exclude falsely elevated measures, we excluded patients whose BP dropped to SBP < 180 mm Hg or DBP < 110 mm Hg within 1 hour of the index severe BP elevation without administration of antihypertensive medications over the same interval. If no repeat BP measurement was available within 1 hour of severe BP elevation, we considered the patient to have severe HTN.

2.3 | Covariates

Demographics, vital signs, body mass index, comorbidities prior to admission (defined per the Elixhauser comorbidity index based on ICD-10 codes[9]), antihypertensive medications, and laboratory results were extracted from the EHR. We defined mean arterial pressure (MAP) as 1/3 SBP + 2/3 DBP. We included coefficient of variation (standard deviation of BP/ mean BP of BP measurements obtained before severe HTN developed) of MAP, SBP, and DBP to account for BP variability. We also included narcotics, sedatives, benzodiazepines, non-steroidal anti-inflammatory drugs (NSAID), corticosteroids, and crystalloid IV fluids; these are markers of pain, anxiety, inflammation, or hypovolemia and have been associated with BP effects.[10–13] Race and ethnicity were extracted from the patient-reported demographic information in the EHR and were included as they have been independently associated with HTN.[14]

2.4 | Antihypertensive treatment definition

Antihypertensive treatment was defined as receiving any oral or IV medication class (angiotensin converting enzyme inhibitors/angiotensin receptor blockers, calcium channel blockers, beta blockers, diuretics, renin inhibitors and vasodilators) within 6 hours of developing severe HTN. Antihypertensive treatment and route were assigned as time-varying covariates within the longitudinal dataset.

2.5 | Outcome

The primary study outcome was time to MAP drop ≥30% within 6 hours from the time of developing severe HTN. For most hypertensive emergencies (patients admitted for severe HTN), guidelines recommend that MAP be decreased gradually by 10–20% in the first hour and a further 5–15% over the next 23 hours to conserve cerebral perfusion and avoid ischemic damage to the vascular beds that have been habituated to elevated BPs.[2,14–16] Additionally, severe BP reductions have been associated with increased risk of death.[17,18] Therefore, we used a MAP cutoff of 30% to reflect a clinically relevant BP drop that

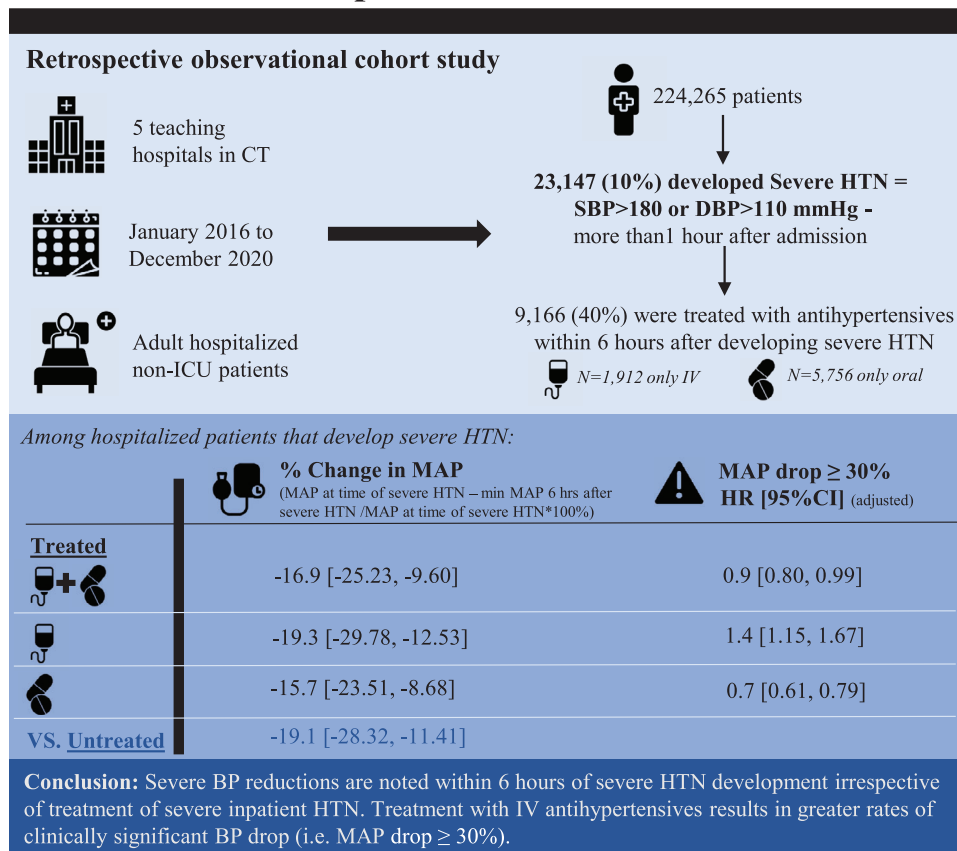# Severe Inpatient Hypertension and Blood Pressure Response to Treatment

Retrospective observational cohort study

5 teaching hospitals in CT

January 2016 to December 2020

Adult hospitalized non-ICU patients

224,265 patients

23,147 (10%) developed Severe HTN = SBP>180 or DBP>110 mmHg - more than 1 hour after admission

9,166 (40%) were treated with antihypertensives within 6 hours after developing severe HTN

N=1,912 only IV   N=5,756 only oral

Among hospitalized patients that develop severe HTN:

	% Change in MAP (MAP at time of severe HTN – min MAP 6 hrs after severe HTN /MAP at time of severe HTN*100%)	MAP drop ≥ 30% HR [95%CI] (adjusted)
Treated (IV + oral)	-16.9 [-25.23, -9.60]	0.9 [0.80, 0.99]
(IV)	-19.3 [-29.78, -12.53]	1.4 [1.15, 1.67]
(oral)	-15.7 [-23.51, -8.68]	0.7 [0.61, 0.79]
VS. Untreated	-19.1 [-28.32, -11.41]	

Conclusion: Severe BP reductions are noted within 6 hours of severe HTN development irrespective of treatment of severe inpatient HTN. Treatment with IV antihypertensives results in greater rates of clinically significant BP drop (i.e. MAP drop ≥ 30%).

FIGURE 1

is better avoided. The secondary outcome was the slope of MAP over 6 hours from the time of initial development of severe HTN.

2.6 | Statistical analysis

Characteristics between patient groups were compared using the χ^2 test for proportions and Wilcoxon rank sum test for continuous variables. Class and number of antihypertensive medications were described. We used Cox proportional hazards models with time-varying covariates to study the association between antihypertensive treatment and time to MAP drop ≥30%. Secondary outcomes included time to SBP drop ≥30% and DBP drop ≥30%. All time-to-event comes were administratively censored at 6 hours. We fit an unadjusted model, reduced adjusted model (with covariates previously shown to be confounders[2,10–14,19] and having a *p* value ≤.05 in our data) and a fully adjusted model (all covariates). We performed similar analysis using the following exposures: (1) treatment with IV antihypertensives versus untreated, (2) treatment with oral antihypertensives versus untreated, and (3) treatment with IV versus oral antihypertensives. For secondary outcomes, we used a linear mixed effect model

with random intercept and random slope at the patient level to study the association between treatment and slope of MAP, SBP and DBP change over 6 hours from the time of severe HTN development in unadjusted and adjusted models.

2.7 | Sensitivity analysis

We conducted several sensitivity analyses. First, severe inpatient HTN was defined as having two consecutive severe BP measurements (SBP > 180 mm Hg or DBP > 110 mm Hg) within 3 hours [sustained BP elevation]. If no repeat BP measurement was available within 3 hours, patient was *not* considered to have severe inpatient HTN. Second, knowing that antihypertensive medications are required in patients who are admitted with CVD diagnosis such as acute coronary symptoms (ACS) or stroke,[20–22] and patients with heart failure and atrial fibrillation may be treated with antihypertensive medications such as loop diuretics and beta blockers[23–25]; we excluded loop diuretics and betablockers from antihypertensive medication list and subsequently stratified by whether patients were admitted for CVD diagnosis (ACS, stroke, heart failure, or atrial fibrillation) or not. Third, treatment was
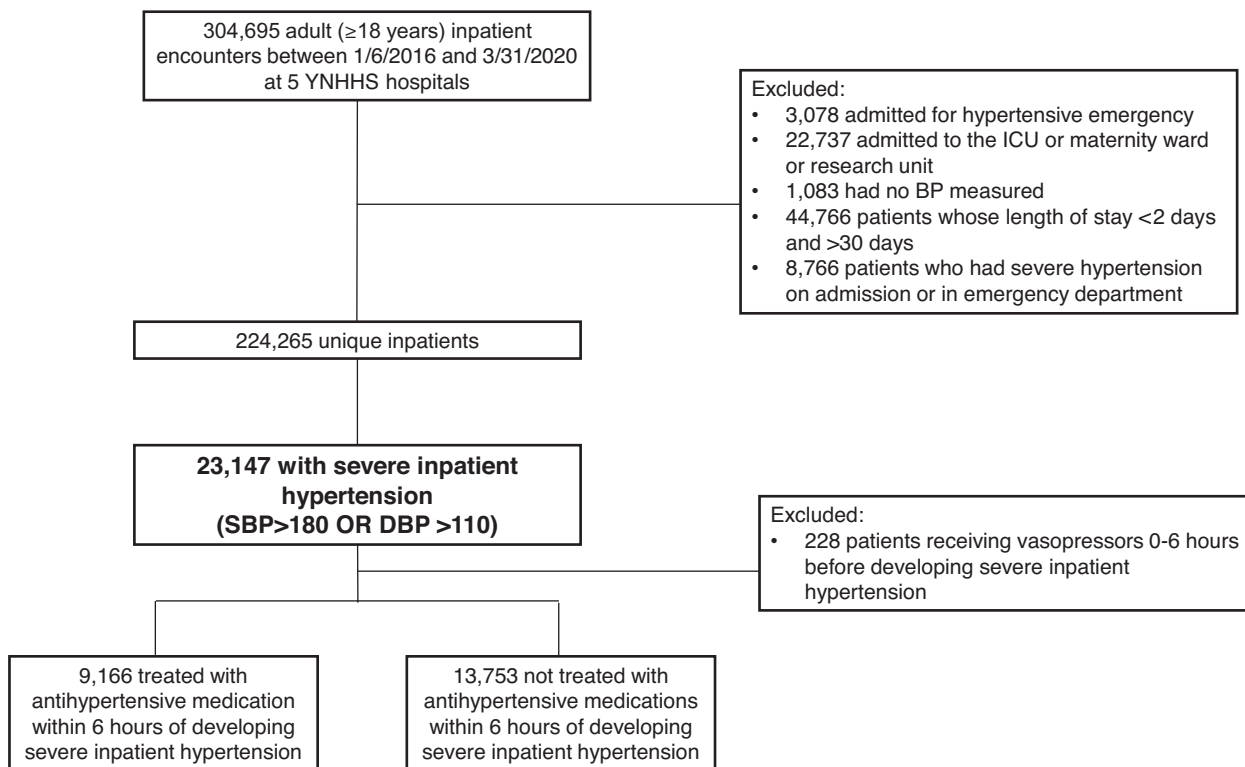
FIGURE 2 Study flow diagram. YNHHS: Yale New Haven Health System; ICU: intensive care unit; BP: blood pressure

defined as receiving a new antihypertensive medication (ie, not a standing medication: medication not prescribed/day ≥90% of their hospital stay). Fourth, we excluded patients admitted to the surgical wards and thus excluded BPs obtained preoperatively and postoperatively. Fifth, we limited our analysis to patients admitted to the medical ward with sustained hypertension and defined treatment as receiving a new medication. Finally, we manually reviewed 100 charts to validate BP measurements, medications and other covariates recorded in our dataset.

Statistical significance was defined by a 2-sided $P < .05$. We conducted our analyses using R, version 4.0.0 (R Project for Statistical Computing).

3 | RESULTS

3.1 | Cohort characteristics

Of the 304 695 adult patient encounters within YNHHS, we identified 224 265 unique patient encounters of which 23 147 developed severe HTN (Figure 3). The median number of BP measurements available was 33 [interquartile range (IQR): 22, 57] during a median length of stay of 4.7 [3.1, 7.4] days. Compared to patients who did not develop severe HTN, those who did were older and more likely to be female, black and be admitted to a medical ward (Table 1). Additionally, those with severe HTN had higher prevalence of comorbidities (*Elixhauser*

score: 6[3, 9] vs. 5[2,9]). Baseline laboratory values were similar though patients with severe HTN had lower estimated glomerular filtration rate (eGFR) [63 vs. 80 ml/min/1.73m^2].[26,27] Admission BPs were higher among patients who developed severe HTN compared to those who did not (MAP: 105 [93, 117] vs. 95 [84, 105]).

After excluding 228 patients who received vasopressors, 9166 received antihypertensive medications while 13 753 were left untreated within 6 hours following severe BP elevation. Median time from admission to first recorded severe BP elevation was 8 [1.3, 49.4] hours overall, 10 [2.2, 53.1] hours among those treated and 7 [1.0, 47.6] among those untreated. Patients who developed severe HTN and received treatment were older, had similar BPs on admission, and had more comorbidities compared to those who were not treated (Table S1). Additionally, treated compared to untreated severe hypertensive patients had similar MAP at time of diagnosis (122 [115, 129]; *p*-value = .04) and were less likely to have received steroids, NSAIDs, crystalloids, or narcotics before severe BP elevation. Moreover, MAP and SBP drop after 6 hours of developing severe BP elevation was higher in untreated than treated inpatients (Figure 3, Table S2). Moreover, treated patients received overall a median of 1 [1, 1.75] antihypertensive; and a median of 0 [0, 1] of new antihypertensives. The most commonly used agents were beta blockers, calcium channel blockers, and angiotensin converting enzyme inhibitors/angiotensin receptor blockers (Table S3). Of the 9166 inpatients who developed severe HTN and were treated within 6 hours, 1912 received IV medications, 5756 received oral medications; and 1498 received both.
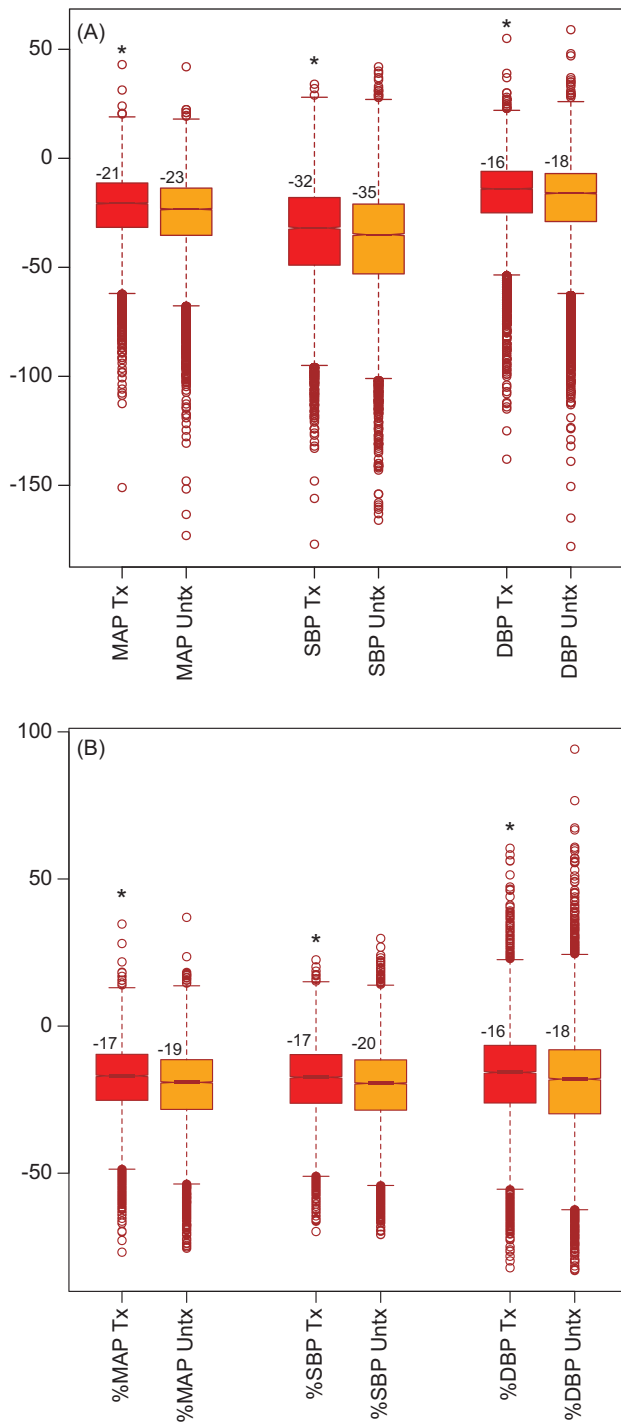
FIGURE 3 (A). Absolute change in blood pressure following severe hypertension development by treatment status. MAP: mean arterial pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure, Tx: treated within 6 hours of developing severe hypertension; Untx: untreated within 6 hours of developing severe hypertension. *: statistically significant difference between treated and untreated (*p* < .001). Median values of absolute change are shown in the figure. Absolute change in blood pressure (MAP, SBP, DBP) 0–6 hours from developing severe inpatient hypertension: blood pressure at time of severe inpatient hypertension – minimum blood pressure recorded within 0–6 hours of developing severe inpatient hypertension. (B). Percent Change in Blood Pressure following Severe Hypertension Development by Treatment Status. MAP: mean arterial

3.2 | Antihypertensive treatment and severe BP drop (≥30%)

Incident MAP drop ≥30% among treated and untreated patients with severe HTN was 2.22/1000 person-hours versus 5.73/1000 person-hours (*p*-value < .001) (Table S2). Among inpatients who developed severe HTN, treatment was associated with lower rates of MAP and DBP drop ≥30% (Table 2) in the fully adjusted model. This is consistent for patients treated with oral medications versus untreated. However, patients who were treated with IV only medications had a 38% (HR, 95%CI: 1.4 [1.2, 1.7]), 43% (1.4 [1.2, 1.7]), and 32% (1.3 [1.1, 1.6]) greater rate of MAP, SBP and DBP drop ≥30% compared to untreated inpatients, respectively, after adjusting for demographic and clinical characteristics. Severe BP drop (≥30%) was also greater among patients treated with IV versus oral medications. The following patient characteristics were associated with greater risk of MAP drop ≥30%: increase in age, congestive heart failure, cardiac arrythmia, peripheral vascular disease, and receiving crystalloids or sedatives.

In sensitivity analysis, in which severe HTN was defined as having sustained BP elevation, we similarly observed that patients who were treated with IV antihypertensives had greater rate of MAP, SBP, and DBP drop ≥30% compared to other groups (Table S4). We then defined treatment as receiving any class of antihypertensive medications except loop diuretics and beta blockers and subsequently stratified our analysis by CVD admission diagnosis (Table S5). In CVD and non-CVD admissions, treatment was associated with a lower rate of DBP drop ≥30% in the fully adjusted models. Treatment with IV medications was associated with greater severe BP drops when compared to other groups. The following sensitivity analyses yielded similar results to the primary analysis: defining treatment as having received a new antihypertensive medication (Table S6), excluding patients admitted to the surgical ward (Table S7), and when considering only patients admitted to the medical ward with sustained hypertension treated with new antihypertensives and adjusting for CVD admission (Table S8).

3.3 | Antihypertensive treatment and BP response

Patients who develop severe HTN and were treated had greater absolute decrease in MAP (-0.6 [−1.0, −0.2]) and DBP (-1.2 [−1.6, −0.8]) compared to untreated inpatients in the fully adjusted model (Table 3). Similarly, patients who received oral antihypertensives compared to no

pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure, Tx: treated within 6 hours of developing severe hypertension; Untx: untreated within 6 hours of developing severe hypertension. *: statistically significant difference between treated and untreated (*p* < .001). All values on y-axis refer to percent change in blood pressures. Median values of percent change are shown in the figure. Percent change in blood pressure (MAP, SBP, DBP) 0–6 hours from developing severe inpatient hypertension: blood pressure at time of severe inpatient hypertension – minimum blood pressure recorded within 0–6 hours of developing severe inpatient hypertension

TABLE 1 Baseline characteristics of study cohort on admission overall and among those who did and did not develop severe inpatient hypertension

	Overall N = 224 265	Among inpatients who developed severe hypertension N = 23 147 (10.3%)	Among inpatients who did not develop severe hypertension N = 201 118 (89.7%)
Demographics			
Age, years	64.7 (18.4)	71.4 (16.3)	63.9 (18.5)
Male	107 130 (47.8)	10 316 (44.6)	96 814 (48.1)
Black	37 441 (16.7)	4576 (19.8)	32 865 (16.3)
Hispanic or Latino	25 839 (11.5)	2341 (10.1)	23 498 (11.7)
Service admitted to			
Medical	178 917 (79.8)	19 021 (82.2)	159 896 (79.5)
Surgical	45 348 (20.2)	4126 (17.8)	41 222 (20.4)
Comorbidities			
Congestive heart failure	59 559 (26.6)	7163 (30.9)	52 396 (26.1)
Cardiac arrhythmia	87 137 (38.9)	9546 (41.2)	77 591 (38.6)
Valvular disease	46 083 (20.5)	4976 (21.5)	41 107 (20.4)
Pulmonary circulation disorder	28 282 (12.6)	2835 (12.2)	25 447 (12.7)
Peripheral vascular disease	49 986 (22.3)	6036 (26.1)	43 950 (21.9)
Hypertension	146 976 (65.5)	18 493 (79.9)	128 483 (63.9)
Paralysis	8938 (4.0)	1122 (4.8)	7816 (3.9)
Other neurological disorder	46 929 (20.9)	6440 (27.8)	40 489 (20.1)
Chronic pulmonary disorders	82 129 (36.6)	8581 (37.1)	73 548 (36.6)
Diabetes	73 770 (32.9)	9791 (42.3)	63 979 (31.8)
Hypothyroidism	43 942 (19.6)	5222 (22.6)	38 720 (19.3)
Renal failure	53 097 (23.7)	7578 (32.7)	45 519 (22.6)
Liver disease	35 717 (15.9)	3390 (14.6)	32 327 (16.1)
Peptic ulcer disease (no bleeding)	10 411 (4.6)	1263 (5.5)	9148 (4.5)
AIDS/HIV	3290 (1.5)	346 (1.5)	2994 (1.5)
Malignancy	51 275 (22.9)	4600 (19.9)	46 675 (23.2)
Rheumatoid arthritis /collagen disorders	17 565 (7.8)	1894 (8.2)	15 671 (7.8)
Coagulopathy	34 507 (15.4)	3133 (13.5)	31 374 (15.6)
Obesity	57 692 (25.7)	5870 (25.4)	51 822 (25.8)
Weight loss	40 080 (17.9)	4250 (18.4)	35 830 (17.8)
Fluid and electrolyte disorders	103 802 (46.3)	12 244 (52.9)	91 558 (45.5)
Blood loss anemia	15 447 (6.9)	1748 (7.6)	13 699 (6.8)
Iron deficiency anemia	42 258 (18.8)	4965 (21.4)	37 293 (18.5)
Alcohol use disorder	28 829 (12.9)	3034 (13.1)	25 795 (12.8)
Drug abuse	30 101 (13.4)	3245 (14.0)	26 856 (13.4)
Psychosis	11 526 (5.1)	1413 (6.1)	10 113 (5.0)
Depression	68 409 (30.5)	7829 (33.8)	60 580 (30.1)
Elixhauser score	5 [2, 9]	6 [3, 9]	5 [2, 9]
Admission characteristics, median [IQR]			
MAP	95.7 [85.0, 106.3]	105.3 [93.0, 117.0]	94.7 [84.3, 105.0]
SBP (mm Hg)	134.0 [118.0, 150.0]	153.0 [134.0, 172.0]	132.0 [117.0, 147.0]
DBP (mm Hg)	76.0 [66.0, 86.0]	80.0 [69.0, 92.0]	76.0 [66.0, 85.0]
Heart Rate (bpm)	85.0 [73.0, 100.0]	82.0 [70.00, 97.00]	85.0 [73.0, 100.0]
BMI (kg/m^2)	27.6 [23.5, 32.9]	27.4 [23.3, 32.5]	27.6 [23.6, 32.9]

(Continues)

TABLE 1 (Continued)

	Overall N = 224 265	Among inpatients who developed severe hypertension N = 23 147 (10.3%)	Among inpatients who did not develop severe hypertension N = 201 118 (89.7%)
Admission laboratory values median [IQR]			
Serum sodium (meq/L)	139.0 [136.0, 141.0]	139.0 [136.0, 141.0]	139.0 [136.0, 141.0]
Serum potassium (meq/L)	4.1 [3.8, 4.05]	4.2 [3.8, 4.6]	4.1 [3.8, 4.5]
Serum chloride (meq/L)	102.0 [98.0, 105.0]	102.0 [98.0, 105.0]	102.0 [98.0, 105.0]
Serum bicarbonate (meq/L)	24.0 [22.0, 27.0]	24.7 [22.0, 27.0]	24.0 [22.0, 27.0]
BUN (mg/dl)	18.0 [12.0, 27.0]	21.0 [14.0, 32.0]	17.0 [12.0, 26.0]
Serum creatinine (mg/dl)	0.9 [0.7, 1.3]	1.1 [0.8, 1.6]	0.9 [0.7, 1.3]
eGFR (ml/min/1.73m^2)	78.5 [49.7, 108.7]	63.3 [38.3, 91.7]	80.3 [51.4, 110.4]
White blood cell count (x1000/ul)	9.1 [6.8, 12.3]	9.0 [6.8, 12.4]	9.2 [6.8, 12.4]
Platelet count (x1000/ul)	223.0 [171.0, 285.0]	224.0 [174.0, 284.0]	223.0 [171.0, 286.0]
Hemoglobin, g/dl	12.0 [10.4, 13.5]	12.0 [10.4, 13.5]	12.0 [10.4, 13.5]
Hematocrit, %	36.9 [32.3, 41.0]	37.0 [32.5, 41.2]	36.9 [32.2, 41.0]

Values are presented as count (percent) or median (IQR).
Abbreviations: BMI, body mass index; BP, blood pressure; MAP, mean arterial pressure; SBP, systolic BP; DBP, diastolic BP; bpm, beats per minute; BUN, Blood Urea Nitrogen; eGFR, Estimated glomerular filtration rate.
p-values are < .0001 for all covariates except chronic pulmonary disorders (*p*-value = .135), obesity (p = .182), iron deficiency anemia (*p*-value = .229), AIDS/HIV (*p*-value = .732), alcohol use disorder (*p*-value = .229), drug abuse (.005), and platelet count (*p*-value = .02).

treatment had greater reduction in MAP and DBP after adjusting for demographic and clinical characteristics. Being older, obese, and having valvular disease were associated with lower MAP drop over time.

In sensitivity analysis, we defined severe HTN as having sustained BP elevation, treatment with IV antihypertensives compared to oral antihypertensives or no treatment was associated with greater BP reduction (Table S9). After defining treatment as receiving any antihypertensive medication class except loop diuretics and beta blockers, we observed that only among non-CVD admission treatment was associated with greater MAP reduction compared to no treatment (Table S10). However, we found that neither treatment administration or route was associated with MAP or SBP changes when defining treatment as receiving new antihypertensive medications (Table S11). Following exclusion of patients admitted to the surgical ward, we found that treatment overall and with IV medications compared to no treatment was associated with lower BP (Table S12). After implementing all exclusion criteria, treatment irrespective of type resulted in greater DBP reduction (Table S13).

4 | DISCUSSION

In this multi-hospital retrospective cohort study, we found that among adults admitted for reasons other than HTN, severe HTN developed in 10% of which 40% received antihypertensive treatment, primarily oral medications. We found that MAP drop ≥30% within 6 hours after severe inpatient HTN development was observed in both untreated and treated patients. After adjusting for demographic and clinical characteristics, untreated patients had greater rates of MAP drop ≥30% compared to treated patients. This association, however, dif-

fered by treatment route. Those treated only with oral antihypertensives within 6 hours of developing severe HTN had lower rates of MAP drop ≥30% compared to untreated patients. In contrast, those treated with IV antihypertensives compared to untreated inpatients had greater rates of MAP drop ≥30%. Absolute reduction in MAP following severe HTN development was slightly greater by 0.6 mm Hg in patients who received treatment (any or oral antihypertensives) compared to untreated.

We found that treatment with oral antihypertensives might be safer than no treatment as it resulted in a lower rate of MAP drop ≥30%. This finding persisted even after including only new medication orders. We hypothesize that a possible mechanism in which oral antihypertensives might cause a lower BP drop compared to no treatment is via blunting of rapid BP response. The most common oral antihypertensives given in this group include metoprolol, amlodipine, and hydralazine. Metoprolol and amlodipine increased baroreflex sensitivity in small scale studies.[28] With improved baroreceptor sensitivity, it is possible that systemic arterial pressure elevation leads to decreased discharge of sympathetic neurons thus resulting in relative bradycardia, decreased cardiac contractility, decreased peripheral vascular resistance, a lower drop in BP, and overall less fluctuation in hemodynamics.[29,30] In contrast, we found that oral antihypertensives resulted in a greater absolute MAP reduction compared to untreated (-0.56 vs. 0.42 mm Hg). The disconnect between the association of treatment on absolute MAP reduction and MAP drop ≥30% might be driven by route of antihypertensive treatment, with oral antihypertensives being safer at reducing MAP over 6 hours. We also observe that the absolute MAP change over 6 hours with IV antihypertensives was +0.42 mm Hg although it resulted in greater severe MAP drop compared to other groups. IV antihypertensives may therefore cause acute reduction in MAP followed

TABLE 2 Association of treatment with MAP, SBP, DBP drop ≥30% over 0–6 hours from time of severe inpatient HTN development

HR (95% CI)	Model 1 (Unadjusted)	Model 2	Model 3
MAP drop ≥ 30%			
Treated versus untreated	0.86 [0.80, 0.94]	0.89 [0.82, 0.96]	0.89 [0.80, 0.99]
Treated with IV only versus untreated	1.49 [1.33, 1.68]	1.49 [1.32, 1.68]	1.38 [1.15, 1.67]
Treated with oral only versus untreated	0.59 [0.53, 0.66]	0.61 [0.54, 0.68]	0.69 [0.61, 0.79]
Treated with IV only versus oral only	2.57 [2.22, 2.98]	2.48 [2.13, 2.91]	2.06 [1.65, 2.57]
SBP drop ≥ 30%			
Treated versus untreated	0.92 [0.86, 0.99]	0.93 [0.86, 1.00]	0.96 [0.87, 1.05]
Treated with IV only versus UNTREATED	1.44 [1.29, 1.62]	1.42 [1.26, 1.59]	1.43 [1.19, 1.71]
Treated with oral only versus untreated	0.69 [0.62, 0.76]	0.69 [0.63, 0.77]	0.78 [0.69, 0.88]
Treated with IV only versus oral only	2.11 [1.84, 2.42]	2.08 [1.80, 2.41]	1.87 [1.53, 2.29]
DBP drop ≥ 30%			
Treated versus untreated	0.79 [0.74, 0.85]	0.82 [0.76, 0.89]	0.79 [0.72, 0.88]
Treated with IV only versus untreated	1.34 [1.20, 1.50]	1.37 [1.22 1.54]	1.32 [1.11, 1.58]
Treated with oral only versus untreated	0.52 [0.47, 0.58]	0.55 [0.49, 0.61]	0.60 [0.53, 0.69]
Treated with IV only versus oral only	2.66 [2.30, 3.08]	2.59 [2.22, 3.02]	2.25 [1.82, 2.78]

Of the 9166 inpatients who developed severe HTN and were treated, 1912 were treated only with IV medications, 5756 were treated only with oral medications and 1498 were treated with a combination of IV and oral medications. 13 753 inpatients developed severe HTN and were not treated.

Model 1: unadjusted; **Model 2**: age, sex, race, ethnicity, ward, comorbidities (congestive heart failure, cardiac arrythmia, peripheral vascular disease, hypertension, diabetes, hypothyroidism, renal failure, AIDS/HIV, cancer, alcohol abuse, drug abuse, psychosis, depression), baseline laboratory values (sodium, potassium, chloride, bicarbonate, BUN, eGFR, WBCC, platelet count, hemoglobin, hematocrit), NSAID use 0–6 hours before time of severe inpatient HTN, crystalloid use 0–6 hours before time of severe inpatient HTN, steroid use 0–6 hours before time of severe inpatient HTN, narcotic use 0–6 hours before time of severe inpatient HTN, sedative use 0–6 hours before time of severe inpatient HTN, hospital.

Model 3: age, sex, race, ethnicity, ward, comorbidities (congestive heart failure, cardiac arrythmia, valvular disease, pulmonary circulation disorder, peripheral vascular disease, hypertension, paralysis, other neurological disorders, chronic pulmonary disease, diabetes, hypothyroidism, renal failure, liver disease, peptic ulcer disease excluding bleeding, AIDS/HIV, lymphoma, cancer, rheumatoid arthritis/collagen disorder, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, blood loss anemia, deficiency anemia, alcohol abuse, drug abuse, psychosis, depression), baseline laboratory values (sodium, potassium, chloride, bicarbonate, BUN, eGFR, WBCC, platelet count, hemoglobin, hematocrit), NSAID use 0–6 hours before time of severe inpatient HTN, crystalloid use 0–6 hours before time of severe inpatient HTN, steroid use 0–6 hours before time of severe inpatient HTN, narcotic use 0–6 hours before time of severe inpatient HTN, sedative use 0–6 hours before time of severe inpatient HTN, maximum MAP before time of severe inpatient HTN development, minimum MAP before time of severe inpatient HTN development, coefficient of variation of MAP before time of severe inpatient HTN development, hospital.

Abbreviations: HR, hazard ratio; CI, confidence interval; MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure, HTN, hypertension; IV, intravenous.

by a plateau thus the acute effect on BP drop might be transient. Our findings might also reflect BP variability during hospitalization; this is influenced by several factors not readily captured in the EHR such as agitation, pain and movement. Additional research to understand the physiological effect of antihypertensives on BP in the inpatient setting are needed.

A recent study of 10 hospitals within the Cleveland Clinic healthcare system assessed whether treatment of inpatient HTN (SBP ≥140 mm Hg) affects outcomes among patients hospitalized for non-CVD reasons.[5] They found that 78% of inpatients had an elevated SBP reading and 33% were treated (IV antihypertensive or a new class of oral antihypertensives). Treatment was associated with greater odds of composite outcome (acute kidney injury [AKI], myocardial injury, stroke) irrespective of treatment route (IV or oral). They observed that among patients with SBP > 160 mm Hg treated and untreated patients had similar rates of SBP decline > 20 mm Hg (58% and 61%, respectively). Similarly, we observed a SBP decrease of -32 [−49, −18] and -25 [−53, −21] mm Hg among treated and untreated inpatients in

our cohort. In the Cleveland Clinic cohort 47% of patients with HTN were treated, compared to 40% of our cohort. There are key differences between our studies. First, our definition for severe HTN relied on higher BP values (SBP > 180 or DBP > 110 mm Hg). In the Cleveland Clinic cohort only 7.7% of untreated and 17.7% of treated inpatients had a SBP≥180 (n = 2,139 vs. 23 147 inpatients in our cohort). Second, we included CVD-related admissions. Third, we defined treatment as receiving any antihypertensive medication within 6 hours of severe HTN development. The main finding from their study was that treatment of elevated BP in the hospital was not beneficial and potentially harmful. Our analyses focused on MAP drop of ≥30% and not on end-organ damage; however, a severe reduction in BP is associated with increased risk of death.[14,17,18] Unlike Rastogi and coworkers we observed that treatment with IV only medications infers additional harm (MAP drop ≥30%) compared to untreated individuals or those treated with oral antihypertensives.[5] Of note, in both cohorts a BP drop was observed irrespective of treatment. This suggests that a one-size-fits-all approach to treatment of severe inpatient HTN is not

TABLE 3 Association of antihypertensive treatment among those who developed severe inpatient hypertension with MAP, SBP, and DBP change within 6 hours of developing severe inpatient hypertension

β (95%CI)	Model 1 (Unadjusted)	Model 2	Model 3
Slope of MAP			
Treated versus Untreated	−0.78 [−1.13, −0.43]	−0.61 [−0.98, −0.25]	−0.56 [−0.97, −0.16]
Treated with IV only versus untreated	−0.93 [−1.73, −0.13]	−0.57 [−1.39, 0.25]	0.42 [−1.49, 0.65]
Treated with oral only versus untreated	−1.02 [−1.47, −0.58]	−0.78 [−1.24, −0.32]	−0.56 [−1.04, −0.08]
Treated with IV only versus oral only	0.51 [−0.31, 1.33]	0.45 [−0.39, 1.29]	0.23 [−0.03, 0.86]
Slope of SBP			
Treated versus Untreated	0.07 [−0.44, 0.58]	−1.07 [−0.63, 0.42]	0.17 [−0.41, 0.76]
Treated with IV only versus untreated	−1.03 [−2.19, 0.13]	−1.16 [−2.35, 0.03]	−1.09 [−2.63, 0.44]
Treated with oral only versus untreated	0.33 [−0.32, 0.99]	0.26 [−0.41, 0.94]	0.66 [−0.39, 1.37]
Treated with IV only versus oral only	−1.48 [−2.71, −0.25]	−1.51 [−2.77, −0.24]	−2.14 [−3.68, −0.62]
Slope of DBP			
Treated versus Untreated	−1.34 [−1.68, −0.99]	−1.03 [−1.38, −0.68]	−1.23 [−1.63, −0.83]
Treated with IV only versus untreated	−1.18 [−1.96, −0.40]	−0.58 [−1.37, 0.22]	−0.58 [−1.64, 0.47]
Treated with oral only versus untreated	−1.85 [−2.29, −1.41]	−1.46 [−1.91, −1.01]	−1.46 [−1.93, −0.98]
Treated with IV only versus oral only	1.39 [0.61, 2.18]	1.41 [0.60, 2.21]	1.40 [0.43, 2.39]

Model 1: unadjusted.
Model 2: age, sex, race, ethnicity, ward, comorbidities (congestive heart failure, cardiac arrythmia, peripheral vascular disease, hypertension, diabetes, hypothyroidism, renal failure, AIDS/HIV, cancer, alcohol abuse, drug abuse, psychosis, depression), baseline laboratory values (sodium, potassium, chloride, bicarbonate, BUN, eGFR, WBCC, platelet count, hemoglobin, hematocrit), NSAID use 0–6 hours before time of severe inpatient HTN, crystalloid use 0–6 hours before time of severe inpatient HTN, steroid use 0–6 hours before time of severe inpatient HTN, narcotic use 0–6 hours before time of severe inpatient HTN, sedative use 0–6 hours before time of severe inpatient HTN, hospital.
Model 3: age, sex, race, ethnicity, ward, comorbidities (congestive heart failure, cardiac arrythmia, valvular disease, pulmonary circulation disorder, peripheral vascular disease, hypertension, paralysis, other neurological disorders, chronic pulmonary disease, diabetes, hypothyroidism, renal failure, liver disease, peptic ulcer disease excluding bleeding, AIDS/HIV, lymphoma, cancer, rheumatoid arthritis/collagen disorder, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, blood loss anemia, deficiency anemia, alcohol abuse, drug abuse, psychosis, depression), baseline laboratory values (sodium, potassium, chloride, bicarbonate, BUN, eGFR, WBCC, platelet count, hemoglobin, hematocrit), NSAID use 0–6 hours before time of severe inpatient HTN, crystalloid use 0–6 hours before time of severe inpatient HTN, steroid use 0–6 hours before time of severe inpatient HTN, narcotic use 0–6 hours before time of severe inpatient HTN, sedative use 0–6 hours before time of severe inpatient HTN, maximum MAP before time of severe inpatient HTN development, minimum MAP before time of severe inpatient HTN development, coefficient of variation of MAP before time of severe inpatient HTN development, hospital.
Abbreviations: CI, confidence interval; MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

appropriate, rather certain patients may especially benefit or be harmed from antihypertensives. Additionally, before initiating treatment we should have further knowledge on how BP is measured in the hospital setting. In our study as well as others looking at inpatient HTN, data on how BP is measured is unavailable. Future studies should use standardized BP measurements (per the AHA guidelines[14]) in the hospital and prospectively assess the effect of treatment on outcomes. Findings from this study will be critical for future inpatient HTN treatment guidelines.

Overall, treatment of acute BP elevations without acute target organ damage with IV antihypertensives has long been discouraged due to harms associated with administration (unpredictable BP reductions, tachycardia) and several quality initiatives to reduce IV medications have been instituted.[2,31–35] A recent study compared receiving as needed antihypertensives following BP elevation (54% given at SBP ≥180 mm Hg) to receiving scheduled home antihypertensives (44% given at SBP: 140–179 mm Hg) on abrupt lowering of BP (SBP drop ≥25%) in hospitalized patients who did not have hypertensive emergency.[8] They found that treatment with IV and not oral as needed

antihypertensives in addition to scheduled antihypertensive compared to treatment with scheduled antihypertensives only resulted in greater odds of SBP drop ≥25% (odds ratio: 2.1[1.6, 2.8] with IV vs. 1.7[0.4, 7.0] with oral). Our study reinforces these findings as treatment with IV antihypertensives was associated with greater rates of MAP drop ≥30% compared to untreated patients or treatment with oral antihypertensives. In our cohort, 40% of inpatients with severe HTN received treatment within 6 hours of BP elevation with 21% receiving only IV antihypertensives. The most common IV antihypertensive administered was hydralazine and the most common oral antihypertensive administered was metoprolol followed by lisinopril. These treatment practices are subjective and not evidence-based.[36,37] Even though there is no substantive evidence that antihypertensive medications improve outcomes of hospitalized patients who develop HTN, physicians believe it is important.[6] This could be due to fear that untreated HTN could progress to end organ damage or healthcare providers not being aware of the risks of overtreatment.[38] However, a retrospective analysis of veterans admitted for non-CVD causes found an increased rate of 30-day adverse events and readmissions as well as

higher 1-year risk of CVD events among patients who had their antihypertensive treatment intensified during inpatient admissions.[39] Additional research is needed to better understand if and when treatment is needed.

Our study has several strengths. To our knowledge, this is the largest cohort of inpatients with severe HTN. We used a set BP cutoff of 180/110 to define severe BP elevation. Participants are well-characterized clinically and encompassed patients admitted for various reasons, allowing for adjustments of many possible confounders (such as comorbidities, medications that affect BP). Results were consistent across multiple sensitivity analysis. We validated our data by manual chart review. There were also limitations: (1) We did not account for outpatient BP before hospitalization. However, we adjusted for history of HTN and for the range of BP fluctuation during the admission before development of severe inpatient HTN; (2) We do not have data on how BP was measured (eg, device, cuff placement). Data represents real word practice; (3) Data is from a single healthcare system and findings might not be generalizable across other healthcare systems; (4) We assessed the effect of antihypertensive treatment by route irrespective of treatment indication, dose, and whether antihypertensive was a home medication. In sensitivity analysis we excluded loop diuretics and beta blockers from antihypertensive medication list as they can be given for other CVD indications and stratified by CVD admission status. Additionally, to account for outpatient antihypertensives, we repeated our analyses in which we excluded standing medications that most likely reflect patients home medications; (5) BP management differs by medical or surgical service patient is admitted to. We excluded patients admitted to the surgical ward in sensitivity analysis; and (6) Other unmeasured covariates might confound the association between treatment of severe HTN and outcomes. We are unable to capture the clinical decision-making reasons for treatment or no treatment (ie, selection bias), and who ordered the antihypertensives. However, we have accounted for all available confounders in the EHR for our analysis. Thus, the greater MAP drop among the untreated may reflect clinical intuition on the part of the providers, that is, providers correctly anticipate BP improvement, that we can't fully capture.

5 | CONCLUSIONS

We found that in a cohort of hospitalized patients admitted for reasons other than HTN, 10% of adults developed severe HTN and 40% of these patients were treated with antihypertensives. Paradoxically, treatment (overall and with oral antihypertensives) compared to no treatment resulted in lower rates of MAP drop ≥30%. Patients with severe HTN treated with only IV antihypertensives compared to untreated and treated with oral only antihypertensives had greater rates of MAP drop ≥30%. Our findings suggest that treating severe inpatient HTN with IV antihypertensives should be done conservatively. Upcoming studies will aim at assessing BP reduction following specific antihypertensive drug classes and types and assess the effect of treatment on clinical outcomes, such as stroke, myocardial infarction and AKI, specifically among those with a significant MAP drop. Given that both untreated

and treated patients with severe HTN had a significant reduction in MAP, a one-size-fits-all approach is not appropriate to treating severe HTN. Additionally, conducting prospective studies using standardized BP measurement to assess frequency of severe HTN as well as the role of treatment on outcomes are critical. Finally, further research is needed to phenotype hospitalized patients with severe HTN based on adverse outcome risk to help establish personalized treatment guidelines.

AUTHOR CONTRIBUTION

Lama Ghazi: Design, Analysis, Writing. Fan Li: Supervision, Analysis, Writing. Xinyuan Chen: Analysis, Writing. Michael Simonov: Data acquisition, Writing. Yu Yamamoto: Data acquisition, Writing. Aditya Biswas: Data acquisition, Writing. Jonathan Hanna: Validation, Writing. Tayyab Shah: Validation, Writing. Raymond Townsend: Writing. Aldo Peixoto: Supervision, Writing. F. Perry Wilson: Supervision, Writing.

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