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# Impact of chronic hypertension on time to goal mean arterial pressure and clinical outcomes in critically ill patients with septic shock requiring vasopressors

Qiu Min Yeo [a,*], Drayton A. Hammond [b], Chenghui Li [c], Keith M. Olsen [c]

[a] Changi General Hospital, 2 Simei Street 3, 529889, Singapore
[b] Rush University Medical Center, Chicago, IL 60612, USA
[c] College of Pharmacy, University of Arkansas for Medical Sciences, 4301 W. Markham, #522, Little Rock, AR 72205, USA

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ABSTRACT

*Purpose:* Mean arterial pressure (MAP) reflects the adequacy of tissue perfusion. In septic shock, vasopressors are recommended to target MAP ≥65 mmHg. The impact of chronic hypertension (HTN) on MAP achievement and outcomes are uncertain.

*Materials and methods:* This retrospective, cohort study compared time to goal MAP in critically ill patients with septic shock admitted between May 2014 and July 2016. Between-group differences of patients with and without HTN were compared using appropriate statistical tests. To adjust for imbalances in baseline characteristics, inverse probability of treatment weighting (IPTW) procedure was performed.

*Results:* Of the 133 included patients, 75 (56.4%) had a history of HTN. Baseline characteristics were mostly similar. Patients with HTN had higher in-hospital (49.3 vs. 31.0%, $p = .035$) and 28-day mortality (53.3 vs. 31.0%, $p = .011$). After weighting and adjustment for imbalanced variables, patients with HTN achieved goal MAP more rapidly than those without (HR: 1.84, 95% CI: 1.14–2.96; $p = .012$). However, they also have higher odds of dying within 28 days of discharge (OR: 3.04, 95% CI: 1.11–8.38; $p = .031$).

*Conclusions:* Patients with HTN achieved goal MAP more rapidly but had higher odds of mortality.



## 1. Introduction

Chronic hypertension is defined as a lasting elevation of blood pressure, which can lead to increased morbidity and mortality due to potential damage to vital organs such as the brain, kidney, and heart [1]. It is the most common comorbidity in patients with severe sepsis and septic shock [2,3]. The pathophysiology of hypertension is complex and incompletely understood but involves various combinations of genetic and physiologic factors. Risk factors of hypertension include age, obesity, family history, race, high-sodium diet, and physical inactivity [4-8]. While there is overwhelming evidence of increasing mortality and morbidity associated with hypertension in the general population, there is little published literature regarding the impact of hypertension on clinical outcomes in patients with septic shock [9].

A multicenter, observational, prospective study evaluated the clinical outcomes of 80 patients with circulatory shock and compared patients who received antihypertensive therapy prior to admission with those who did not [10]. The investigators found that patients who received antihypertensive therapy prior to admission had lower norepinephrine requirements, which was not statistically significant, throughout admission. They also found significantly shorter duration of mechanical ventilation and intensive care unit (ICU) length of stay. The investigators concluded that the difference in clinical outcomes suggest a protective effect of prior to admission antihypertensive therapy. Another recently published retrospective, cohort study investigated the effects of chronic exposure to antihypertensive therapies on cumulative vasopressor dosing in 133 patients with septic shock [11]. Although there was no difference in cumulative vasopressor dose among four study groups at 48 h, all patients receiving chronic antihypertensives had lower total time on vasopressors than patients not on antihypertensives prior to admission. There is a possibility that patients with hypertension have higher basal blood pressures, which may help them attain a target mean arterial pressure (MAP) faster than those without hypertension. MAP is a weighted average of the systolic and diastolic blood pressures, which may serve as a reasonable surrogate marker for adequacy of tissue perfusion when invasive measurements of these variables are unavailable [12].

The 2016 Surviving Sepsis Campaign guidelines recommend initiation of vasopressors to target MAP of at least 65 mmHg in patients

* Corresponding author.
*E-mail addresses:* Qmyeo.uams@gmail.com, qiu_min_yeo@cgh.com.sg (Q.M. Yeo), Drayton_hammond@rush.edu (D.A. Hammond), cli@uams.edu (C. Li), kolsen@uams.edu (K.M. Olsen).

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with septic shock to optimize the supply of oxygen to meet cellular oxygen demand [13]. There is currently no literature describing the time to goal MAP of at least 65 mmHg in critically ill patients with septic shock and a history of hypertension. The objective of this study was to evaluate the impact of hypertension (determined using information from electronic documentation) on outcomes in patients with and without hypertension who developed septic shock requiring vasopressors.

## 2. Methods

### 2.1. Setting

This single-center, retrospective cohort study was conducted in critically ill patients admitted to the medical or surgical ICU at an urban, academic medical center from May 2014 to July 2016. There was no formal protocol for vasopressor initiation for patients with septic shock in the institution between May 2014 and October 2015; however, vasopressor initiation was protocolized between November 2015 and July 2016. According to protocol, norepinephrine was initiated as monotherapy between November 2015 and February 2016, and vasopressin was started at 0.04 units/min within four hours of norepinephrine initiation between March 2016 and July 2016 [14,15].

### 2.2. Patient selection

Patients were included if they were at least 18 years old, admitted to an ICU for at least 48 h, and diagnosed with septic shock requiring vasopressors. Septic shock is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation [16]. Patients who were pregnant; on midodrine, pseudoephedrine, or fludrocortisone before or after the diagnosis of septic shock; or had a past medical history of orthostatic hypotension or adrenal insufficiency were excluded from the study. Patients were determined as having hypertension if documented in their past medical history or admission notes.

### 2.3. Outcomes

The primary outcome was the time to achieving and then maintaining a MAP of at least 65 mmHg for at least four hours without the need for additional blood pressure support during ICU stay [14,15]. Secondary outcomes were duration of vasopressor use, days free of vasopressor support, mortality, and ICU and hospital lengths of stay. Use of antihypertensive agents prior to admission, vasopressor requirements during ICU stay, and need for hydrocortisone were compared between the two groups.

**Table 1**
Baseline patient characteristics with sepsis stratified by hypertension and without hypertension, before and after inverse probability treatment weighting.

| Baseline characteristic | Unweighted | | | | Weighted | | | |
|---|---|---|---|---|---|---|---|---|
| | Hypertension (n = 75) | No hypertension (*n* = 58) | p-value | Standardized Difference | Hypertension (*n* = 74.6) | No hypertension (*n* = 49.3) | p-value | Standardized Difference |
| Age, years (mean ± SD) | 62.8 ± 14.5 | 56.2 ± 14.9 | 0.011 | 44.8 | 61.9 ± 13.8 | 59.2 ± 13.8 | 0.284 | 19.5 |
| Weight, kg (mean ± SD) | 92.0 ± 27.0 | 83.4 ± 24.7 | 0.059 | 33.5 | 87.7 ± 24.6 | 87.6 ± 28.1 | 0.992 | 0.2 |
| Gender, male, n (%) | 36 (48.0%) | 33 (56.9%) | 0.309 | −17.9 | 55.2% | 56.1% | 0.935 | −1.8 |
| Race, n (%) | | | 0.568[a] | | | | 0.990 | |
| White | 47 (62.7%) | 41 (70.7%) | | −17.1 | 70.5% | 69.1% | | 2.9 |
| African American | 24 (32.0%) | 14 (24.1%) | | 17.6 | 24.7% | 25.9% | | −2.7 |
| Others | 4 (5.3%) | 3 (5.2%) | | 0.7 | 4.8% | 5.0% | | −0.8 |
| Admission unit, n (%) | | | 0.868 | | | | 0.978 | |
| MICU | 54 (72.0%) | 41 (70.7%) | | 2.9 | 76.0% | 76.3% | | −0.5 |
| SICU | 21 (28.0%) | 17 (29.3%) | | −2.9 | 24.0% | 23.8% | | 0.5 |
| SOFA score within 6 h of ICU admission (mean ± SD) | 9.2 ± 3.2 | 9.7 ± 3.1 | 0.425 | −14.0 | 9.1 ± 2.8 | 9.3 ± 3.2 | 0.732 | −6.4 |
| APACHE II score at 24 h of ICU admission (mean ± SD) | 27.7 ± 9.2[b] | 27.1 ± 8.8 | 0.706 | 6.7 | 26.6 ± 8.4[b] | 27.3 ± 8.4 | 0.662 | −8.0 |
| Comorbidities, n (%) | | | | | | | | |
| Ischemic heart disease | 21 (28.0%) | 2 (3.5%) | <0.001[a] | 71.6 | 17.1% | 6.3% | 0.165 | 34.2 |
| Chronic heart failure | 18 (24.0%) | 8 (13.8%) | 0.141 | 26.3 | 28.4% | 25.0% | 0.770 | 7.7 |
| Obstructive lung disease | 17 (22.7%) | 6 (10.3%) | 0.062 | 33.7 | 18.2% | 12.5% | 0.420 | 15.9 |
| Chronic Kidney Disease | 21(28.0%) | 5(8.6%) | 0.007[a] | 51.8 | 18.3% | 9.5% | 0.198 | 25.6 |
| CKD without long-term dialysis | 18 (24.0%) | 5 (8.6%) | 0.022[a] | 42.6 | 15.0% | 9.5% | 0.381 | 16.9 |
| CKD requiring long-term dialysis | 3 (4.0%) | 0 (0.0%) | 0.257[a] | 28.9 | 3.2% | 0.0% | 0.134 | 25.9 |
| Advanced liver disease | 9 (12.0%) | 10 (17.2%) | 0.392 | −14.9 | 13.7% | 19.5% | 0.468 | −15.7 |
| Diabetes | 32 (42.7%) | 5 (8.6%) | <0.001[a] | 84.7 | 28.5% | 22.9% | 0.600 | 12.9 |
| Cancer | 31 (41.3%) | 22 (37.9%) | 0.691 | 7.0 | 42.6% | 40.0% | 0.811 | 5.2 |
| Autoimmune disease | 4 (5.3%) | 1 (1.7%) | 0.386[a] | 19.7 | 3.4% | 1.5% | 0.455 | 12.3 |
| Positive culture, n (%) | 34 (45.3%) | 25 (43.1%) | 0.797 | 4.5 | 46.3% | 43.2% | 0.776 | 6.3 |
| Non-lactose fermenting Gram negative bacilli, n (%) | 18 (24.0%) | 10 (17.2%) | 0.343 | 16.8 | 20.1% | 20.8% | 0.935 | −1.7 |
| Multidrug-resistant organism, n (%) | 18 (24.0%) | 9 (15.5%) | 0.228 | 21.4 | 24.9% | 14.9% | 0.278 | 25.1 |
| Source of infection, n (%) | | | | | | | | |
| Unknown | 16 (21.3%) | 16 (27.6%) | 0.403 | −14.6 | 21.3% | 21.4% | 0.989 | −0.2 |
| CNS | 1 (1.3%) | 1 (1.7%) | 1.000[a] | −3.2 | 0.8% | 1.7% | 0.584 | −8.1 |
| Lungs | 24 (32%) | 17 (29.3%) | 0.739 | 5.8 | 32.8% | 28.4% | 0.681 | 9.6 |
| Intra-abdominal | 7 (9.3%) | 4 (6.9%) | 0.755[a] | 8.9 | 10.9% | 8.0% | 0.667 | 9.7 |
| Skin/skin structure | 9 (12.0%) | 3 (5.2%) | 0.229[a] | 24.6 | 11.2% | 5.4% | 0.323 | 21.1 |
| Urine | 9 (12.0%) | 11 (19.0%) | 0.265 | −19.4 | 8.5% | 25.7% | 0.015 | −46.9 |
| Line/blood | 8 (10.7%) | 5 (8.6%) | 0.775[a] | 6.9 | 13.4% | 6.7% | 0.270 | 22.2 |
| Other | 2 (2.7%) | 2 (3.5%) | 1.000[a] | −4.5 | 2.4% | 3.8% | 0.671 | −7.9 |

SD: standard deviation; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; CNS: central nervous system; MICU: medical intensive care unit; SICU: surgical intensive care unit; SOFA: sequential organ failure assessment.

[a] Fisher's exact test.

[b] n = 74.

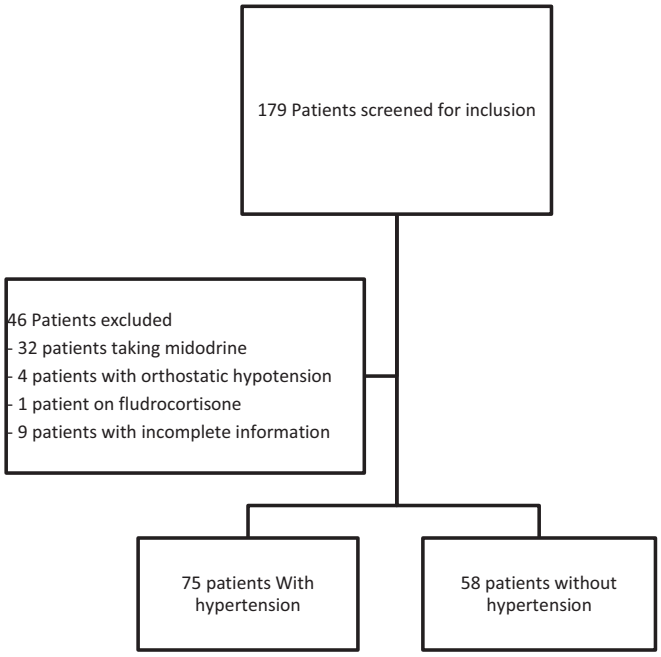


**Fig. 1.** Patient inclusion and exclusion with a diagnosis of septic shock with or without hypertension.

### 2.4. Sample size determination

Using data from an unpublished internal study, assuming a median time from onset of septic shock to goal MAP of 10 h in patients with chronic hypertension and 12 h in patients without chronic hypertension, a total of 126 patients would provide a power of 80% to detect a difference in the primary outcome at a two-sided alpha level of 0.05.

### 2.5. Analysis

Patient baseline characteristics (Table 1) were compared using Student's *t*-test or Wilcoxon Rank Sum test (if distribution is skewed) for continuous variables and Pearson's Chi-square test or Fisher's exact test for categorical variables. To adjust for imbalances in baseline characteristics, inverse probability of treatment weighting (IPTW) procedure was performed, where weights were the inverse of the probabilities to be in the hypertension group, estimated based on baseline demographic and clinical characteristics of patients (age, gender, race, body weight, admission ICU unit, SOFA score within 6 h of ICU admission, APACHE score within 24 h of ICU admission, lactate peak in the first 6 h before and after vasopressor initiation, weight-adjusted volume, comorbidities [ischemic heart disease, congestive heart failure, obstructive Lung disease, chronic kidney disease, advanced liver disease, diabetes, autoimmune disease], and positive culture) using logistic regression [17]. Stabilized weights were used to reduce the influence of extreme weights [18]. Balance in baseline characteristics after IPTW was assessed using weighted *t*-test or Chi-square test and standardized differences [19,20]. A standardized difference < 10 indicates balance in the baseline characteristic [21]. Outcomes variables after IPTW were compared using weighted regressions, adjusting for any baseline characteristics with a standardized difference of ≥ 10 after IPTW. Cox-proportional regression model was used for time to goal MAP. Proportional hazards assumption was tested on the basis of Schoenfeld residuals after fitting the Cox model and was not violated ($p = .9851$) [22]. For patients who did not achieve goal MAP, time to goal MAP was censored at either death within ICU, ICU discharge, or the time when use of all vasopressors were stopped, whichever occurred the earliest. Linear regression was used for durations of ICU and hospitalization and logistic regression was used for inpatient mortality and mortality at 28 days after discharge. All analyses were performed with Stata version 14 (StataCorp, College Station, TX). A *p*-value <.05 was deemed statistically significant. This study was approved by the University's Institutional Review Board (approval number 205838).

## 3. Results

### 3.1. Baseline characteristics

Of the 133 patients who were included, 75 (56.4%) had a history of hypertension (Fig. 1). Baseline characteristics were similar between groups except patients with hypertension were older (62.8 vs. 56.2 y, $p = .011$), received less resuscitation fluid within six hours of initiating vasopressor (19.5 vs. 29.1 ml/kg, $p = .037$) and more frequently had ischemic heart disease (28.0 vs. 3.5%, $p < .001$), diabetes (42.7 vs. 8.6%, $p < .001$), and chronic kidney disease without long-term dialysis (24.0 vs. 8.6%, $p = .022$). Almost half of the patients in both groups were male with a mean APACHE II score of 27 and mean SOFA score within six hours of ICU admission of nine. Approximately 70% of the patients received care in the medical ICU. After IPTW, none of the baseline characteristics were statistically significant except for urinary source of infection but standardized differences were ≥10 for age; ischemic heart disease; chronic kidney disease with/without dialysis; multidrug resistant organism; obstructive lung disease; advanced liver disease; diabetes; autoimmune disease; skin, line and urinary source of infection; and weight-adjusted volume of resuscitation fluids received within six hours of initiating vasopressors, suggesting remaining imbalance in baseline characteristics (Tables 1 and 4).

**Table 2**
Primary and secondary outcomes in septic patients with or without hypertension.

| | Unweighted | | | Weighted | | |
|---|---|---|---|---|---|---|
| Variable | Hypertension ($n = 75$) | No Hypertension (n = 58) | p-value[b] | Hypertension (n = 74.6) | No Hypertension (n = 49.3) | p-value* |
| Time to goal MAP, hours (Median, IQR) | 7.2 (3.3–15.6)[a] | 8.9 (3.1–15.2) | 0.9 | 6.0 (2.5–12.3) | 10.0 (3.1–15.2) | 0.296 |
| Duration of vasopressor use, hours (Mean ± SD) | 70.6 ± 65.6 | 84.7 ± 97.0 | 0.321 | 86.1 ± 76.2 | 87.2 ± 94.2 | 0.958 |
| Days free of cardiovascular support (Mean ± SD) | 14.6 ± 19.6 | 20.4 ± 24.5 | 0.131 | 15.0 ± 17.8 | 17.0 ± 22.0 | 0.567 |
| Mortality during hospitalization, n (%) | 37 (49.3%) | 18 (31.0%) | 0.035 | 50.20% | 27.30% | 0.025 |
| Mortality at 28 days, n (%) | 40 (53.3%) | 18 (31.0%) | 0.011 | 52.70% | 27.30% | 0.014 |
| ICU duration, days (Mean ± SD) | 6.6 ± 6.1 | 9.9 ± 10.0 | 0.024 | 7.7 ± 6.7 | 9.1 ± 9.0 | 0.42 |
| Hospital duration, days (Mean ± SD) | 17.5 ± 20.2 | 23.9 ± 26.3 | 0.115 | 18.6 ± 18.4 | 20.7 ± 23.7 | 0.576 |

IQR: Interquartile range; SD: standard deviation; MAP: mean arterial pressure; ICU: intensive care unit.
[a] $n = 73$; two subjects with time to goal MAP =0 were excluded from this analysis.
[b] Unweighted *p*-value from regression adjusting for hypertension only without weighting.
* Weighted *p*-values from weighted regressions adjusting for hypertension only.

**Table 3**
Regression analysis of primary and secondary outcomes comparing patients with hypertension and those without hypertension. Weighted column reports results from weighted regressions adjusting for hypertension only.

| | Unweighted | | | | Weighted | | | | Weighted & Adjusted for Variables with Standardized Difference ≥10 After IPTW | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cox proportional regression | HR | 95%CI | | p | HR | 95%CI | | p | HR | 95%CI | | p |
| Time to goal MAP, hours | 1.02 | 0.72 | 1.46 | 0.900 | 1.23 | 0.84 | 1.80 | 0.296 | 1.84 | 1.14 | 2.96 | 0.012 |
| Logistic regression | OR | 95%CI | | p | OR | 95%CI | | p | OR | 95%CI | | p |
| Mortality during hospitalization | 2.16 | 1.06 | 4.43 | 0.035 | 2.69 | 1.13 | 6.40 | 0.025 | 2.69 | 0.99 | 7.31 | 0.052 |
| Mortality during 28 days | 2.54 | 1.24 | 5.21 | 0.011 | 2.97 | 1.25 | 7.05 | 0.014 | 3.04 | 1.11 | 8.38 | 0.031 |
| Linear regression | Coeff | 95%CI | | | Coeff | 95%CI | | | Coeff | 95%CI | | |
| Duration of vasopressor use, hours | −14.05 | −41.99 | 13.88 | 0.321 | −1.11 | −42.37 | 40.15 | 0.958 | 3.08 | −34.91 | 41.08 | 0.873 |
| Days free of cardiovascular support | −5.81 | −13.38 | 1.76 | 0.131 | −2.00 | −8.89 | 4.89 | 0.567 | 0.05 | −6.79 | 6.89 | 0.989 |
| ICU duration, days | −3.21 | −5.99 | −0.43 | 0.024 | −1.38 | −4.76 | 2.00 | 0.420 | −1.15 | −4.34 | 2.04 | 0.476 |
| Hospital duration, days | −6.40 | −14.38 | 1.58 | 0.115 | −2.05 | −9.26 | 5.17 | 0.576 | 0.18 | −6.80 | 7.15 | 0.960 |

Weighted & Adjusted column reports results from weighted regressions adjusting for all variables with standardized difference ≥10 after IPTW (hypertension, age, ischemic heart disease, chronic kidney disease with/without dialysis, multidrug-resistant organism, urine infection, obstructive lung disease, advanced liver disease, diabetes, autoimmune disease, and skin and line infection and weight-adjusted volume).

### 3.2. Primary and secondary outcomes

Time to goal MAP (hypertension vs. no hypertension, median (Interquartile range [IQR]): 7.2 (3.3–15.6) vs. 8.9 h (3.1–15.2), $p = .90$), duration of vasopressor use (70.7 ± 65.6 vs. 84.7 h ± 97.0, $p = .32$), and days free of vasopressor support (14.6 ± 19.6 vs. 20.4 d ± 24.5, $p = .13$) were similar between groups. Patients with hypertension had higher in-hospital (49.3 vs. 31.0%, $p = .035$) and 28-day mortality (53.3 vs. 31.0%, $p = .011$). Duration of ICU stay was shorter (6.6 ± 6.1 vs. 9.9 d ± 10.0, $p = .024$) in patients with hypertension, but hospital lengths of stay were similar (17.5 ± 20.2 vs. 23.9d ± 26.3, $p = .12$). After IPTW, duration of ICU stay was no longer significantly different (7.7 ± 6.7, 9.1 ± 9.0, $p = .42$) but in-hospital (50.2 vs. 27.3%, $p = .025$) and 28-day mortality (52.7 vs. 27.3%, $p = .014$) remained higher in patients with hypertension. However, after further adjusting for aforementioned baseline characteristics that remained imbalanced after IPTW, time to goal MAP ($p = .012$) became significant and 28-day mortality ($p = .031$) remained significant (Table 2). After weighting and adjustment for imbalanced variables, patients with chronic hypertension were more likely to achieve goal MAP than those who did not have chronic hypertension (HR: 1.84, 95% CI: 1.14–2.96; p = .012) (Table 3, Fig. 2). However, they also had higher odds of dying within 28 days of discharge (OR: 3.04, 95% CI: 1.11–8.38; p = .031). After weighting and adjustment for imbalanced variables, mortality during hospitalization, duration of vasopressor use, days free of cardiovascular support, duration of ICU stay, and duration of hospitalization were not affected by patients' history of hypertension.

### 3.3. Other clinical outcomes

A non-significantly lower proportion of the patients with hypertension required mechanical ventilation (76.0%) compared to those without (84.5%), $p = .23$. However, duration of mechanical ventilation was significantly shorter in patients with hypertension (5.0 ± 4.7 vs. 8.5 d ± 9.1, $p = .013$). In both groups, a similar proportion of patient used etomidate as an induction agent (Table 4).

### 3.4. Antihypertensive agents

Almost 90% of the patients with a history of hypertension were taking antihypertensive agents prior to admission, with many of them (40.0%) being on one antihypertensive agent and 28.0% of them on two antihypertensive agents. The most common antihypertensive agent used in patients with hypertension prior to admission was a beta-blocker (49.3%), followed by an angiotensin-converting-enzyme inhibitor (32.0%). In contrast, only 12.1% of the patients without a history of hypertension were on antihypertensive agents for other indications such heart failure and portal hypertension (Table 5).

### 3.5. Vasopressor and corticosteroid requirements

The vasopressor requirements for patients in both groups were similar regarding the specific vasopressors prescribed. All patients received norepinephrine during ICU admission, and vasopressin was the second most frequently prescribed vasopressor (hypertension vs. no hypertension: 76.0 vs. 81.0%). The maximum rate of vasopressors required and duration of time on vasopressors were not significantly different between groups. One-third of the patients in each group required a total daily hydrocortisone dose of at least 200 mg for similar durations of time (71.0 ± 73.0 vs. 100.1 h ± 166.1, $p = .44$) (Table 4).

## 4. Discussion

In the management of septic shock, adequate fluid resuscitation precedes the initiation of vasopressors. Although the volume of adequate fluid resuscitation varies between individual, most patients require at least 30 ml/kg of fluids initially [13]. In this single-center, retrospective cohort study involving critically ill patients with septic shock requiring

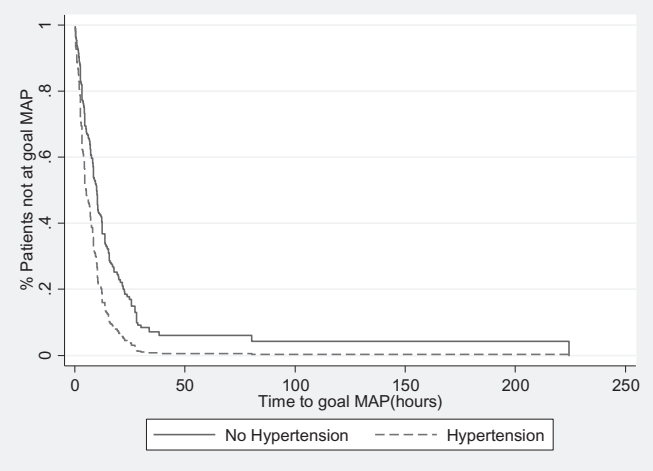


**Fig. 2.** Survival curve based on estimates from weighted cox proportional hazard regression of time to goal MAP*

**Table 4**
Clinical variables of septic patients with or without hypertension.

| Variable | Patients with hypertension ($n = 75$) | Patients without hypertension ($n = 58$) | p-value |
|---|---|---|---|
| Volume of resuscitation fluid administered within 6 h of initiating vasopressor, mL (mean ± SD) | 1640.7 ± 1451.2 | 2175.8 ± 2051.9 | 0.081 |
| No. of patients receiving at least 200 mg of hydrocortisone/day, n (%) | 24 (32.0%) | 22 (37.9%) | 0.48 |
| Duration of hydrocortisone use of at least 200 mg/day, hours (mean ± SD), among users | 71.0 ± 73.0 | 100.1 ± 166.1 | 0.44 |
| Weight adjusted volume, ml/kg (mean ± SD) | 19.5 ± 17.6 | 29.1 ± 33.9 | 0.0367 |
| Mechanical ventilation, n (%) | 57 (76.0%) | 49 (84.5%) | 0.23 |
| Duration of mechanical ventilation, days (mean ± SD), among users | 5.0 ± 4.7 | 8.5 ± 9.1 | 0.013 |
| No of patients who used etomidate as induction agent, n (%) | 29 (38.7%) | 28 (48.3%) | 0.27 |
| New renal replacement therapy, n (%) | 18 (24.0%) | 11 (19.0%) | 0.49 |
| Hemodialysis | 4 (22.2%) | 2 (18.2%) | 1.0[a] |
| Continuous renal replacement therapy | 9 (50.0%) | 5 (45.5%) | |
| Both hemodialysis and continuous renal replacement therapy | 5 (27.8%) | 4 (36.4%) | |

SD: standard deviation.
[a] Fisher's exact test.

vasopressors, septic patients with chronic hypertension more rapidly achieved and maintained goal MAP compared to those without despite smaller weight-based volumes of intravenous fluid resuscitation. This paradoxical finding suggests that patients with chronic hypertension may have begun to recover to their own chronic baseline blood pressure, which may be higher than 65 mmHg, after initial fluid resuscitation. Interestingly, one study found that all patients receiving chronic antihypertensives had less total time on vasopressors than patients not on antihypertensive therapy prior to admission [11]. Our findings are in line with their conclusions and point to a possibility that the improvement in blood pressure may have started at an earlier phase of recovery.

Patients with chronic hypertension are known to have high peripheral vascular resistance due to alterations in structure, mechanical properties, and function of small arteries [23,24]. They may also be more sensitive to norepinephrine – a result of greater vasoconstrictor responses to norepinephrine as noradrenergic receptors are not downregulated when subjected to increased circulating norepinephrine levels [25]. These inherent differences may explain the more rapid attainment and maintenance of goal MAP in hypertensive patients.

**Table 5**
Antihypertensive agents prior to admission in patients with sepsis and with or without hypertension.

| | Patients with hypertension ($n = 75$) | Patients without hypertension ($n = 58$) | p-value |
|---|---|---|---|
| Number of antihypertensive agents at baseline, n (%) | | | <0.001 |
| None | 9 (12.0%) | 51 (87.9%) | |
| One | 30 (40.0%) | 4 (6.9%) | |
| Two | 21 (28.0%) | 2 (3.5%) | |
| Three | 13 (17.3%) | 1 (1.7%) | |
| Four | 1 (1.3%) | 0 | |
| Five | 1 (1.3%) | 0 | |
| Type of antihypertensive agents[a], n (%) | | | |
| Angiotensin-converting-enzyme inhibitors | 24 (32.0%) | 1 (1.7%) | <0.001 |
| Angiotensin receptor blocker | 8 (10.7%) | 0 | 0.010 |
| Alpha-blocker | 2 (2.7%) | 0 | 0.504 |
| Beta-blocker | 37 (49.3%) | 4 (6.9%) | <0.001 |
| Thiazide diuretic | 9 (12.0%) | 0 | 0.005 |
| Dihydropyridine calcium channel blocker | 15 (20.0%) | 0 | <0.001 |
| Non-dihydropyridine calcium channel blocker | 1 (1.3%) | 0 | 1 |
| Nitrate | 6 (8.0%) | 1 (1.7%) | 0.137 |
| Other antihypertensive | 18 (24.0%) | 4 (6.9%) | 0.009 |

[a] Fisher's exact test.

Although the use of etomidate as an induction agent in patients who required mechanical ventilation can potentially affect blood pressure, the proportion of patients who used etomidate as an induction agent was similar in both groups. Hence, we do not believe the use of etomidate affected our results.

Faster achievement and maintenance of goal MAP did not translate to lower mortality in this study. On the contrary, patients with hypertension had higher odds of 28-day mortality in regression analysis. Although the APACHE II scores were similar at baseline, 28-day mortality was significantly higher in patients with hypertension before and after IPTW adjustments. This brings about another widely debated controversy as to whether patients with chronic hypertension may require MAP targets which are higher than 65 mmHg [26,27]. Hypotension in septic shock results in hypoperfusion, which leads to organ failure. It is hypothesized that the autoregulatory mechanism to maintain blood flow into organs over a constant range of blood pressure in healthy individuals is impaired in septic shock [28]. Hence, blood pressure needs to increase to maintain organ perfusion in patients with septic shock. Furthermore, the threshold of autoregulation is dependent on a patient's baseline blood pressure, which tends to be higher in patients with a history of chronic hypertension [29]. Although higher MAP targets did not result in reduced mortality in a heterogeneous patient population, it has been associated with lower rates of acute kidney injury in patients with chronic hypertension [26]. It is unknown if targeting a higher MAP would reduce the mortality rate in septic shock patients with chronic hypertension, but it is certainly an ongoing debate which warrants further investigation. In the meantime, more aggressive interventions for primary prevention and management of hypertension in general populations may indirectly mitigate negative outcomes such as mortality in critically ill patients.

The primary study endpoint evaluated the amount of time required to achieve and maintain goal MAP for at least four hours, which allows for any re-equilibration of intravascular fluids or true needs of end organ perfusion to be recognized and accounted for in the rate of the vasopressor infusion. Other studies have used time to goal MAP as a primary outcome [14,15,30]. A single-center, retrospective, cohort study of medical ICU patients with septic shock found that the median time to goal MAP was 2 h in the group which received norepinephrine and had vasopressin added when the norepinephrine dose was 10 μg/min or greater [30]. This was much lower than what we found in our study but was most likely because patients were not required to maintain goal MAP for at least four hours. Another study found similar times to goal MAP (6 to 10 h) as observed in this study [14].

The utilization patterns of vasopressors were in accordance with guidance from the 2016 Surviving Sepsis Campaign guidelines, suggesting that the main findings of the study were not a result of deviation from key recommendations and would be generalizable to patient

populations of similar demographic profiles [13]. The study also met the calculated sample size, suggesting that our study was not underpowered to find a difference in time to goal MAP if one truly existed between the groups. IPTW was performed to control for baseline differences. The IPTW approach weights individuals based on their propensity score, with those patients who receive the typical treatment decision being weighted down as they are overrepresented in the data [20]. This serves to make the sample more representative of the overall population. Some weaknesses of the study include it being retrospective and single-center in nature, and the accuracy of the data obtained from the electronic system relies on the meticulous collection by clinicians taking care of the patients. Also, home medications and documentation of hypertension were assumed to accurately reflect each patient's hypertensive status. As a result, the most recent dosage of an antihypertensive agent could not be determined with certainty in every patient. We acknowledge that information regarding time to antibiotics or the appropriateness of use was not collected. Given the known impact of antibiotics on mortality in sepsis, there is a possibility that this may have affected our findings. However, we do not expect this to be significantly different between groups as there was no major change in workflows or practices within the study period.

## 5. Conclusion

This is the first study investigating the impact of hypertension on time to achieve and maintain a goal blood pressure in critically ill patients with septic shock requiring vasopressors. Patients with chronic hypertension achieved and maintained goal MAP more rapidly but had higher odds of mortality. Further evaluation into the effects of hypertension and the optimal target MAP on mortality in critically ill patients are needed. Future research should also focus on identifying treatable factors to increase survival.

## Grant numbers and/or funding information

Not applicable.

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