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VASOPRESSOR-RESISTANT HYPOTENSION, COMBINATION VASOPRESSOR THERAPY, AND SHOCK PHENOTYPES IN CRITICALLY ILL ADULTS WITH VASODILATORY SHOCK

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ABSTRACT—**Objective:** To examine the risk factors, resource utilization, and 1-year mortality associated with vasopressor-resistant hypotension (VRH) compared with vasopressor-sensitive hypotension (VSH) among critically ill adults with vasodilatory shock. We also examined whether combination vasopressor therapy and patient phenotype were associated with mortality. **Design:** Retrospective cohort study. **Setting:** Eight medical-surgical intensive care units at the University of Pittsburgh Medical Center, Pittsburgh, PA. **Patients**: Critically ill patients with vasodilatory shock admitted between July 2000 and October 2008. **Interventions**: None. **Measurements and Main Results:** Vasopressor-resistant hypotension was defined as those requiring greater than 0.2 μg/kg per minute of norepinephrine equivalent dose of vasopressor consecutively for more than 6 h, and VSH was defined as patients requiring ≤0.2 μg/kg per minute to maintain MAP between 55 and 70 mm Hg after adequate fluid resuscitation. Of 5,313 patients with vasodilatory shock, 1,291 patients (24.3%) developed VRH. Compared with VSH, VRH was associated with increased risk of acute kidney injury (72.7% vs. 65.0%; $P < 0.001$), use of kidney replacement therapy (26.0% vs. 11.0%; $P < 0.001$), longer median (interquartile range [IQR]) intensive care unit length of stay (10 [IQR, 4.0–20.0] vs. 6 [IQR, 3.0–13.0] days; $P < 0.001$), and increased 1-year mortality (64.7% vs. 34.8%; $P < 0.001$). Vasopressor-resistant hypotension was associated with increased odds of risk-adjusted mortality (adjusted odds ratio [aOR], 2.93; 95% confidence interval [CI], 2.52–3.40; $P < 0.001$). When compared with monotherapy, combination vasopressor therapy with two (aOR, 0.91; 95% CI, 0.78–1.06) and three or more vasopressors was not associated with lower mortality (aOR, 0.93; 95% CI, 0.68–1.27). Using a finite mixture model, we identified four unique phenotypes of patient clusters that differed with respect to demographics, severity of illness, processes of care, vasopressor use, and outcomes. **Conclusions:** Among critically ill patients with vasodilatory shock, VRH compared with VSH is associated with increased resource utilization and long-term risk of death. However, combination vasopressor therapy was not associated with lower risk of death. We identified four unique phenotypes of patient clusters that require further validation.

KEYWORDS—Epidemiology, mortality, vasopressor-resistant hypotension, vasopressor-sensitive hypotension

INTRODUCTION

Vasodilatory shock, the most common form of shock in critically ill patients, is characterized by decreased vasomotor tone, preserved or elevated cardiac output, and hypotension that persists despite adequate fluid resuscitation (1). Vasopressors are frequently used to restore vasomotor tone and maintain blood pressure. However, when hypotension persists despite use of high dose of vasopressors, the patient is deemed to be vasopressor-resistant. Currently, there are no consensus definitions for what constitutes vasopressor resistance, and observational studies (2), as well as clinical trials (3,4), have used a threshold dose of greater than 0.2 μg/kg per minute of norepinephrine equivalent to be indicative of vasopressor resistance. However, the epidemiology, resource utilization, and long-term outcomes associated with greater than 0.2 μg/kg per minute of norepinephrine equivalent are uncertain.

Catecholamines, such as norepinephrine, epinephrine, dopamine, and phenylephrine, and noncatecholamine vasopressors, such as vasopressin, selepressin, and angiotensin II, are frequently used in the treatment of vasodilatory shock either individually or in

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various combinations. Combination vasopressor therapy is hypothesized to raise MAP and treat shock more effectively than monotherapy (4), and current approaches to vasodilatory shock management recommend multimodal "broad-spectrum vasopressors" compared with stepwise vasopressor dose escalation (5). However, the long-term outcomes associated with combination vasopressor therapy compared with monotherapy are unclear.

Emerging evidence suggests that underlying patient phenotype may be associated with outcomes. For instance, genetic variations in *ARDβ$_2$* (β2-adrenergic receptor gene) encoding of β2-adrenergic receptor have been found to be associated with a higher norepinephrine requirement and increased mortality (6). Similarly, variants in AGTRAP, the angiotensin II receptor type 1–associated protein, have been associated with reduced MAP, lower vascular tone, and an increased mortality (7). More recently, phenotypes of cardiogenic shock have been described that have distinct associations with mortality (8). Whether patient phenotypes are associated with outcomes in patients with vasodilatory shock is unclear.

Using a large cohort of critically ill patients with vasodilatory shock, we performed the following analyses. First, we examined the frequency, risk factors, resource utilization, and risk-adjusted 1-year mortality associated with vasopressor-resistant hypotension (VRH) compared with vasopressor-sensitive hypotension (VSH). Second, we tested the hypothesis of whether combination vasopressor therapy is associated with lower risk-adjusted mortality compared with monotherapy. Third, we performed a phenotype analysis of patients with vasodilatory shock and explored association with risk-adjusted 1-year mortality.

MATERIALS AND METHODS

Data source and study population

We conducted a retrospective cohort study using the University of Pittsburgh Medical Center intensive care unit (ICU) database: the High-Density Intensive Care data set, details of which have been published elsewhere (9–11). The study population included adults admitted to medical, cardiac, abdominal transplant, cardiothoracic, surgical, neurovascular, neurotrauma, and trauma ICUs during July 2000 through October 2008. More detailed description of study population is in the Supplement (eMethods 1, http://links.lww.com/SHK/B500). The University of Pittsburgh's Human Research Protection Office approved the study and waived the need for informed consent.

We included patients 18 years or older with vasodilatory shock requiring vasopressors despite adequate i.v. volume resuscitation. We defined vasodilatory shock as cardiac index greater than 2.3 L/min per 1.73 m^2 or central venous pressure (CVP) greater than 8 cm of H_2O in the preceding 18 h and following 6 h after initiation of vasopressor support to maintain MAP between 55 and 70 mm Hg after receiving fluid resuscitation of greater than 25 mL/kg (4). We excluded patients if they were not receiving vasopressors; those who had a history of or current hospital admission with a diagnosis of acute coronary syndrome or heart failure; those requiring extracorporeal membrane oxygenator; patients with liver failure as evidenced by the Model for End-Stage Liver Disease score greater than 30; those with missing data on fluids, cardiac index, or CVP; and pregnant women.

Definitions

Primary exposure variable was VRH, defined as those who required a total sum vasopressor dose of greater than 0.2 μg/kg per minute of norepinephrine equivalent for a minimum period of 6 continuous hours and a maximum of 48 h to maintain a MAP between 55 and 70 mm Hg after receiving greater than 25 mL/kg of volume resuscitation in the preceding 24 h of diagnosis of VRH (4). Vasopressor-sensitive hypotension was defined as those patients requiring vasopressors ≤0.2 μg/kg per minute of norepinephrine equivalents to maintain MAP between 55 and 70 mm Hg after receiving greater than 25 mL/kg of volume resuscitation. All vasopressor doses were standardized in terms of norepinephrine equivalents (Supplementary Table 1, http://links.lww.com/SHK/B500) (1,4,12,13).

Outcomes

The primary outcome was 1-year mortality from the index ICU admission, and mortality data were obtained from the Social Security Death Master File (14). Secondary outcomes included hospital mortality, acute kidney injury (AKI), use of kidney replacement therapy, dependence on kidney replacement therapy, and hospital and ICU length of stay. Kidney replacement therapy dependence data at 1 year were obtained from the US Renal Data System (15).

Variables

The following data were extracted for each patient: demographics; body mass index; comorbid conditions; admission to medical or surgical service; admission for liver transplantation; presence of trauma; need for mechanical ventilation; time from ICU admission to initiation of vasopressor therapy; presence of sepsis identified using the *International Classification of Diseases, Ninth Revision* code; and Acute Physiology and Chronic Health Evaluation (APACHE) III score following ICU admission on a scale of 0 to 299, with higher score indicating greater severity of illness. Severity of organ dysfunction assessed by Sequential Organ Failure Assessment (SOFA) score on a scale of 0 to 4 for each organ, with higher score indicating more severe organ dysfunction. We also extracted hemodynamic data including the volume of i.v. fluids administered, hourly MAP, cardiac index, CVP, and type and dose of vasopressor used for each patient.

For patients with missing age (n = 1) and cumulative fluid balance (n = 630), we used the MICE (multivariable imputation by chained equation) method (16) to impute missing values using the following variables as predictors: age, history of diabetes, history of hypertension, APACHE III score, surgical admission, cumulative norepinephrine equivalents, use of mechanical ventilation, AKI stage, median MAP, admission for liver transplantation, admission for trauma, sepsis, race, sex, Charlson comorbidity index, time from ICU admission to vasopressor initiation, cumulative fluid balance, reference creatinine, and mortality. Patients were classified as AKI according to the maximum Kidney Disease Improving Global Outcomes criteria based on serum creatinine, urine output, or both within 7 days from ICU admission (17).

Statistical analysis

We compared baseline patient characteristics, processes of care, resource utilization, and outcomes of patients with VRH and VSH. Categorical variables were compared using chi-square test and continuous variables using one-way ANOVA and Kruskal-Wallis test. We assessed 1-year survival using Kaplan-Meier failure plots and compared using log-rank test. We fitted multivariable logistic regression and estimated risk-adjusted odds ratios (aORs) with corresponding 95% confidence intervals (CIs) for association of VRH with 1-year mortality compared with VSH (reference). In these models, we adjusted for differences in age, sex, race, Charlson comorbidity score, history of hypertension, history of diabetes, APACHE III score, admission to surgical service, admission for liver transplantation, time from ICU admission to initiation of vasopressors, use of mechanical ventilation, median MAP during the 6 h of treatment with vasopressors, and cumulative fluid balance during ICU stay. We also examined the association between a range of vasopressor doses and risk-adjusted 1-year mortality.

We classified patients as receiving combination or monotherapy based on the number of vasopressors administered during the first 6 h of treatment of shock. To examine the association of combination vasopressor therapy versus monotherapy on risk-adjusted mortality, we fitted multivariable logistic regression models adjusting for age, sex, race, Charlson comorbidity score, history of hypertension, use of mechanical ventilation, APACHE III score, AKI severity within 7 days of ICU admission, median dose of norepinephrine equivalents, and median MAP in the first 6 h of vasopressor therapy.

For phenotyping of patients with vasodilatory shock, we conducted latent class analysis using finite mixture models (18) to identify class membership of patients exposed to vasopressors. In these models, we hypothesized that underlying unobservable patient clusters exist with varying survival when exposed to various vasopressor combinations. Models were fitted using standardized norepinephrine dose equivalents as an outcome and vasopressor combination as predictors while using covariates such as APACHE III, age, and sex that model the probability of class membership. Optimal numbers of clusters were determined using Bayesian information criteria. We then examined vasopressor combination, clinical characteristics, and mortality by patient clusters and explored the association of clusters with 1-year mortality adjusting for age, sex, race, APACHE III, and standardized dose of vasopressors and cumulative fluid balance using logistic regression. Statistical analyses were performed using R version (4.0) using R Studio and Stata 16.0 (StataCorp, College Station, TX). Finite mixture models were performed using Stata 16.0 (StataCorp). All hypothesis tests were 2-sided with a significance level of $P < 0.05$.

RESULTS

Population characteristics

Of 45,877 patients, we excluded patients younger than 18 years (n = 309), those with a diagnosis of acute coronary syndrome

(n = 6,227), pregnant women (n = 12), those who use extracorporeal membrane oxygenator (n = 48), those with a MELD score greater than 30 (n = 1,508), those with cardiogenic shock or postoperative heart failure (n = 33); those who never required vasopressors (n = 28,982), and patients with missing data on MAP (n = 253). Of 8,505 patients who received vasopressors, we excluded patients who received less than 25 mL/kg of fluid resuscitation (n = 30), those with missing fluid data (n = 373), those with missing both CVP and cardiac index data (n = 2,517), patients with cardiac index $_{of}$ 2.3 L/min per 1.73 m^2 or less (n = 200), and patients with CVP less than 8 cm H_2O (n = 72). Of 5,313 patients who required vasopressors and formed the analysis cohort, 24.3% (n = 1,291) met the criteria for VRH (Fig. 1).

Median age was 61 years (interquartile range [IQR], 50.0–72.0 years), and 42.6% were females (Table 1). The vast majority of patients had septic shock in both the groups (97.7%). Median APACHE III score was 75.0 (IQR, 54.0–99.0). Patients with VRH were young (median age, 58.0 vs. 62.0 years; $P < 0.001$) and less likely to be White compared with patients with VSH. There were subtle differences in body mass index and Charlson comorbidity index between the two groups. Patients in the VRH group had lower prevalence of hypertension (33.3% vs. 37.7%; $P = 0.005$), had diabetes (17.5% vs. 21.6%; $P = 0.002$), were more likely to be admitted to the medical service (36.4% vs. 27.6%; $P < 0.001$), and were less likely to be admitted for liver transplantation (3.9% vs. 8.1%; $P < 0.001$). Patients with VRH were more severely ill with a median APACHE III score (88.0 [IQR, 63.0–112.0] vs. 72.0 [IQR, 52.0–94.7]; $P < 0.001$), had more severe organ dysfunction with higher total SOFA score (21 [IQR, 14.0–31.0] vs. 13 [IQR, 7.0–22.0]; $P < 0.001$), and required mechanical ventilation (80.2% vs. 77.5%; $P = 0.047$) on day 1 of ICU admission. Patients with VRH received more fluids in the preceding 24 h (7.5 [IQR, 2.7–15.5] vs. 3.8 [IQR, 0.95–8.2] liters; $P < 0.001$) and had higher median CVP (20 cm vs. 17 cm H_20; $P < 0.001$) and cardiac index (3.8 vs. 3.6 L/min per BSA; $P < 0.001$) in the preceding 24 h (Table 1). Median time from ICU admission to meeting criteria for VRH and VSH was as follows: 29.0 versus 9.7 h; $P < 0.001$. Patients with VRH had lower median MAP during the first 6 h of vasopressor use (69.5 vs. 73.2 mm Hg; $P < 0.001$) and required higher median cumulative dose of vasopressors for the first 6 h (0.24 μg/kg per minute [IQR, 0.20–0.33 μg/kg per minute] vs. 0.04 μg/kg per minute [IQR, 0.02–0.09 μg/kg per minute] of norepinephrine equivalents; $P < 0.001$). Figure 2 shows the distribution of vasopressor combinations used stratified by total norepinephrine equivalents, and Supplementary Table 2 (http://links.lww.com/SHK/B500) shows the distribution of vasopressor type and dose by VRH and VSH.

Association of VRH with outcomes

Patients with VRH had more fluid overload compared with patients with VSH (median cumulative fluid balance, 7.7 vs. 3.8 L; $P < 0.001$; Table 2). There was a higher risk of stage III AKI (39.5% vs. 21.1%; $P < 0.001$) and need for kidney replacement therapy (26.0% vs. 11.0%; $P < 0.001$) compared with patients with VSH. Patients with VRH had higher resource utilization including median ICU (10.0 days [IQR, 4.0–20.0 days] vs. 6.0 days [IQR, 3.0–13.0 days], $P < 0.001$) and hospital length of stay (20.0 days [7.0–39.0 days] vs. 17.0 days [9.0–31.0 days]; $P < 0.001$). The crude mortality at 30 days (47.7% vs. 18.2%; $P < 0.001$), 90 days (57.2% vs. 26.1%; $P < 0.001$), 180 days (61.3% vs. 30.4%; $P < 0.001$), and at 1 year (64.7% vs. 34.8%; $P < 0.001$) was higher among patients with VRH (Fig. 3(A)).

Using multivariable logistic regression, development of VRH was associated with nearly threefold higher odds of 1-year

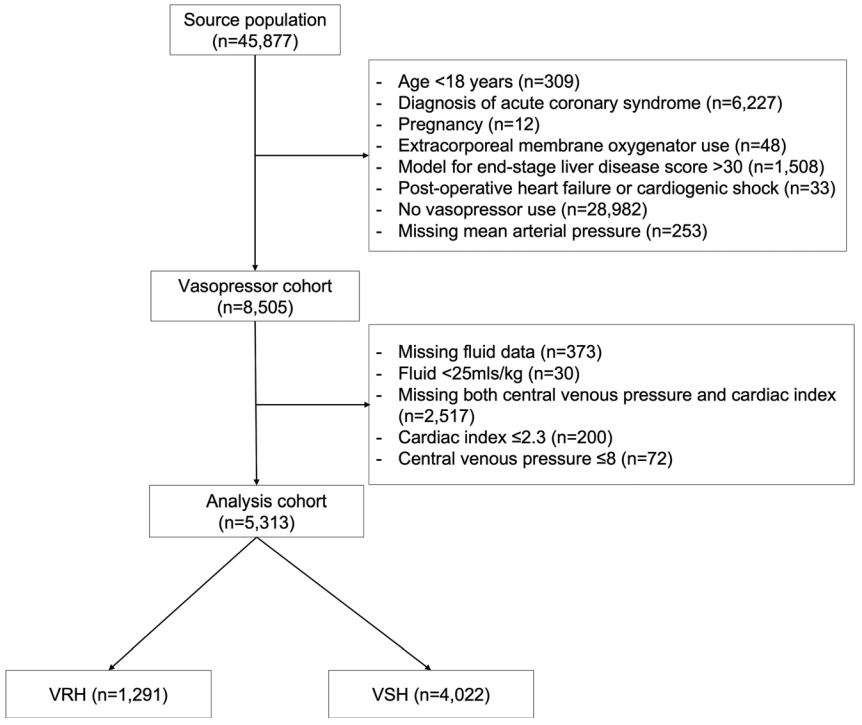

FIG. 1. **Flow diagram showing selection of study population.**

TABLE 1. **Baseline characteristics of study population**

Characteristics	No. (%) All patients (n = 5,313)	VRH (n = 1,291)	VSH (n = 4,022)	*P*
Age, median (IQR), y	61 (50.0–72.0)	58.0 (48.0–71.0)	62.0 (51.0–72.0)	<0.001
Age category, y				
18–44	828 (15.6)	253 (19.6)	575 (14.3)	<0.001
>44–54	1,003 (18.9)	271 (21.0)	732 (18.2)	
>54–64	1,254 (23.6)	294 (22.8)	960 (23.9)	
>64–74	1,215 (22.9)	266 (20.6)	949 (23.6)	
>74–84	841 (15.8)	177 (13.7)	664 (16.5)	
>84	172 (3.2)	30 (2.3)	142 (3.5)	
Female sex	2,261 (42.6)	550 (42.6)	1,711 (42.5)	0.97
Race				
White	4,235 (79.7)	988 (76.5)	3,247 (80.7)	0.008
African American	342 (6.4)	95 (7.4)	247 (6.1)	
Other	142 (2.7)	35 (2.7)	107 (2.7)	
Unknown	594 (11.2)	173 (13.4)	421 (10.5)	
BMI, median (IQR), kg/m^2	26.6 (23.0–30.8)	25.9 (22.3–30.4)	26.8 (23.3–30.9)	<0.001
Charlson score, median (IQR)	3.0 (2.0–5.0)	3.0 (1.0–5.0)	3.0 (2.0–5.0)	0.001
Charlson category				
0	680 (12.8)	215 (16.7)	465 (11.6)	<0.001
1	1,387 (26.1)	346 (26.8)	1,041 (25.9)	
2	1,731 (32.6)	372 (28.8)	1,359 (33.8)	
3	1,515 (28.5)	358 (27.7)	1,157 (28.8)	
Comorbid conditions				
Hypertension	1,946 (36.6)	430 (33.3)	1,516 (37.7)	0.005
Diabetes	1,093 (20.6)	226 (17.5)	867 (21.6)	0.002
Cardiac disease	1,260 (23.7)	307 (23.8)	953 (23.7)	0.98
Vascular disease	566 (10.7)	126 (9.8)	440 (10.9)	0.25
Liver disease	528 (9.9)	126 (9.8)	402 (10)	0.84
Chronic obstructive pulmonary disease	607 (11.4)	147 (11.4)	460 (11.4)	0.96
Malignancy	177 (3.3)	49 (3.8)	128 (3.2)	0.32
Liver transplantation	200 (3.8)	52 (4.0)	148 (3.7)	0.62
Chronic kidney disease	541 (10.2)	140 (10.8)	141 (10.0)	0.39
APACHE III score, median (IQR)*	75 (54.0–99.0)	88.0 (63.0–112.0)	72.0 (52.0–94.7)	<0.001
Cumulative SOFA score in the preceding 24 h, Median (IQR)	15.0 (8.0–24.0)	21.0 (14.0–31.0)	13.0 (7.0–22.0)	<0.001
Surgical admission	3,734 (70.3)	821 (63.6)	2,913 (72.4)	<0.001
Admission for liver transplantation	377 (7.1)	50 (3.9)	327 (8.1)	<0.001
Trauma admission	487 (9.2)	127 (9.8)	360 (9.0)	0.34
Known baseline serum creatinine, median (IQR), mg/dL	1.0 (0.80–1.40)	1.0 (0.80–1.50)	1.0 (0.80–1.40)	0.15
Reference creatinine, median (IQR), mg/dL	0.90 (0.80–1.1)	0.90 (0.8–1.12)	0.90 (0.8–1.1)	0.46
Baseline eGFR, median (IQR), mL/min per 1.73 m^2	75.0 (68.9–94.7)	75.0 (70.7–98.6)	75.0 (68.5–93.9)	0.27
Sepsis	5,192 (97.7)	1,267 (98.1)	3,925 (97.6)	0.29
Mechanical ventilation*	4,152 (78.1)	1,035 (80.2)	3,117 (77.5)	0.047
Fluid received in the preceding 24 h, median (IQR), L	4.5 (1.30–9.9)	7.5 (2.7–15.5)	3.8 (0.95–8.2)	<0.001
CVP in the preceding 24 h, median (IQR), cm H_2O	17.0 (13.0–22.0)	20.0 (15.0–26.0)	17.0 (13.0–21.0)	<0.001
Cardiac index in the preceding 24 h, L/min per BSA	3.6 (3.0–4.5)	3.8 (3.2–4.7)	3.6 (3.0–4.3)	<0.001
MAP during the first 6 h of vasopressor use,† median (IQR), mm Hg	72.5 (66.5–79.5)	69.5 (64.0–77.0)	73.2 (67.0–80.0)	<0.001
Time from ICU admission to vasopressor initiation, median (IQR), h	12.3 (3.8–64.5)	29.0 (8.3–162.7)	9.7 (2.8–42.0)	<0.001
Cumulative vasopressor dose during the first 6 h,‡ median (IQR), NE	0.07 (0.03–0.18)	0.24 (0.20–0.33)	0.04 (0.02–0.09)	<0.001

*Day 1 of ICU admission.

†MAP was calculated during the 6 h for patient with VRH and VSH.

‡Vasopressors were standardized in terms of NE equivalents (supplement) (4,13). Cumulative dose of vasopressors during the first 6 h for patients with VRH and VSH.

BMI, body mass index; eGFR, estimated glomerular filtration rate; NE, norepinephrine equivalent units.

mortality (aOR, 2.93; 95% CI, 2.52–3.40; $P < 0.001$; Hosmer-Lemeshow goodness-of-fit C statistic 0.17) (Table 3). Using vasopressor dose as a continuous variable, every increase in vasopressor dose of 0.01 μg/kg per minute was associated with 37.8% risk of death (aOR, 4.97; 95% CI, 3.54–6.99; $P < 0.001$; Fig. 3B).

When compared with monotherapy, combination therapy with two (aOR, 0.91; 95% CI, 0.78–1.06) or three or more (aOR, 0.93; 95% CI, 0.68–1.27) vasopressors was not associated with risk-adjusted mortality (Table 4). Among the subgroup of patients who received vasopressor dose greater than 0.2 μg/kg per minute, combination vasopressor therapy of two (aOR, 0.74; 95% CI, 0.56–0.97) or three or more (aOR, 0.73; 95% CI, 0.50–1.08) vasopressors was not associated with risk-adjusted mortality compared with monotherapy.

Association of patient phenotype with outcomes

We identified four unique patient clusters that differed with respect to patient demographics, severity of illness, processes of care, and outcomes (Supplementary Tables 3 [http://links.lww.

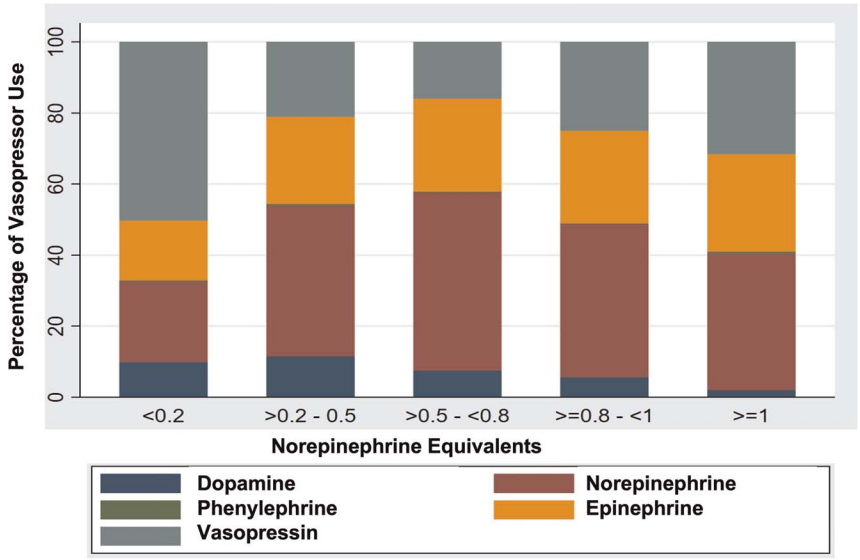

FIG. 2. **Distribution of vasopressor combinations used**. Figure showing the distribution of vasopressors used stratified by total dose of norepinephrine equivalents.

com/SHK/B500] and 4 [http://links.lww.com/SHK/B500]). Compared with cluster 1, patients in clusters 2, 3, and 4 were younger; had more comorbid conditions; and were more severely ill. Patients in cluster 3 were severely ill, were more likely to be mechanically ventilated, were more likely to have a history of liver disease and liver transplantation, were admitted to medical service, have oliguria, have lower median MAP, receive more fluids and have higher cumulative fluid balance, have higher CVP and cardiac index, and receive higher dose of vasopressors than patients in other clusters (Supplementary Table 5, http://links.lww.com/SHK/B500). There were significant variations in type of vasopressor use (Fig. 4) and the dose of vasopressors (Supplementary Table 5, http://links.lww.com/SHK/B500) by clusters.

The ICU and hospital length of stay, use of kidney replacement therapy, and crude 1-year mortality also varied by clusters (Supplementary Table 4, http://links.lww.com/SHK/B500). Patients in cluster 3 were more likely to receive kidney replacement therapy (27%) and also have higher 1-year mortality (64.9%) than patients in other clusters (Fig. 5; Supplementary Table 4, http://links.lww.com/SHK/B500). Compared with cluster 1, patients in cluster 3 (aOR, 2.17; 95% CI, 1.77–2.65) and cluster 4 (aOR, 1.40; 95% CI, 1.18–1.66) had incremental risk of death after adjusting for differences in age, sex, race, dose of norepinephrine equivalents, APACHE III score, and cumulative fluid balance (Table 5).

DISCUSSION

In this large heterogeneous cohort of critically ill patients with persistent vasodilatory shock following adequate volume resuscitation, the prevalence of VRH was 24.3% using a vasopressor dose of norepinephrine equivalent equal to or greater than 0.2 μg/kg

TABLE 2. **Resource utilization and outcomes**

Variable	No. (%)			*P*
	All patients (n = 5,313)	VRH (n = 1,291)	VSH (n = 4,022)	
Cumulative fluid balance, Liters, median (IQR)	4.4 (1.3–10.0)	7.7 (2.7–15.3)	3.8 (1.0–8.4)	<0.001
Development of AKI*				
Stage I	839 (17.6)	176 (15.4)	663 (18.4)	<0.001
Stage II	1,889 (39.7)	369 (32.2)	1,520 (42.1)	
Stage III	1,213 (25.5)	453(39.5)	760 (21.1)	
Use of KRT	780 (14.7)	336 (26.0)	444 (11.0)	<0.001
KRT dependence at 1 y	10 (0.2)	2(0.2)	8 (0.2)	0.75
Digital ischemia	779 (14.7)	183 (14.2)	596 (14.8)	0.57
Digital necrosis	288 (5.4)	62 (4.8)	226 (5.6)	0.26
Length of stay, median (IQR), d				
ICU	6.0 (3.0–15.0)	10.0 (4.0–20.0)	6.0 (3.0–13.0)	<0.001
Hospital	18.0 (9.0–33.0)	20.0 (7.0–39.0)	17.0 (9.0–31.0)	0.14
Mortality				
30-d	1,346 (25.3)	616 (47.7)	730 (18.2)	<0.001
90-d	1,790 (33.7)	739 (57.2)	1,051 (26.1)	<0.001
6 mo	2,014 (37.9)	791 (61.3)	1,223 (30.4)	<0.001
1 y	2,236 (42.1)	835 (64.7)	1,401 (34.8)	<0.001

*According to the maximum KDIGO stage within 7 days of ICU admission.
KRT, kidney replacement therapy.

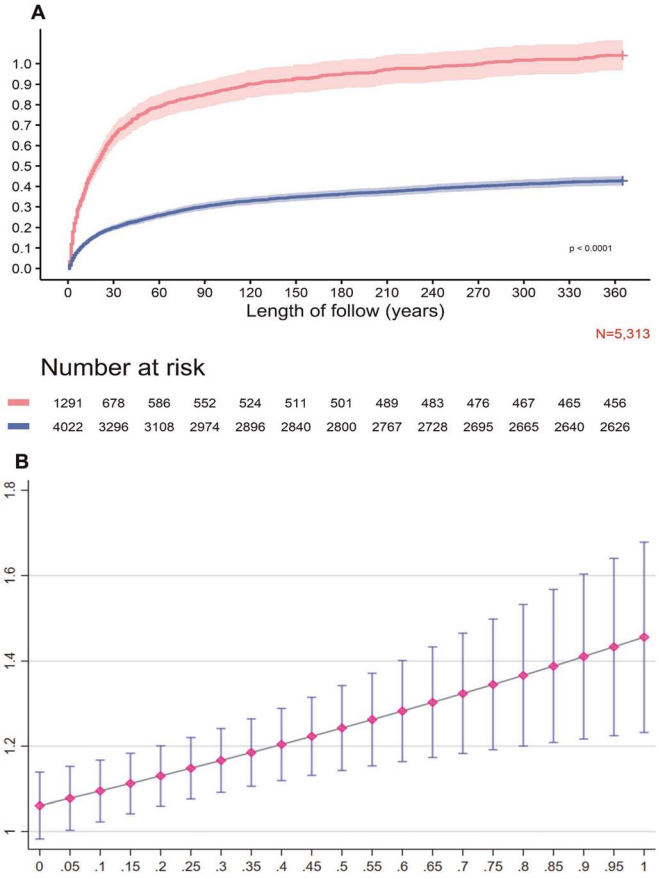

FIG. 3. **Association between VRH and mortality**. A, The Kaplan-Meier failure plots for probability of crude mortality over 1 year from ICU admission among patients with VRH compared with VSH. Red line represents VRH, blue line represents VSH, and shading represents 95% CI. The probability of death was lower among patients who had VSH compared with VRH (log-rank $P < 0.001$). B, Figure showing aOR with corresponding 95% CIs for 1-year mortality across a range of vasopressor doses. The models were adjusted for age sex, race, Charlson comorbidity score, history of hypertension, use of mechanical ventilation, APACHE III score, total SOFA score, AKI severity within 7 days of ICU admission, median dose of norepinephrine equivalent dose, and median MAP in the first 6 h of vasopressor therapy. Every increase in norepinephrine equivalents 0.01 μg/kg per minute was associated with 37.8% higher odds of death.

per minute to define VRH. Development of VRH was associated with increased risk of AKI, use of mechanical ventilation, kidney replacement therapy, and 1-year risk-adjusted mortality compared with patients with VSH. Our study also found that combination vasopressor therapy was not associated with lower risk of death compared with patients with monotherapy after accounting for the dose of vasopressors and severity of hypotension. We identified four unique patient clusters that varied by patient characteristics, processes of care, severity of illness, and clinical outcomes.

A unique finding of our study is that VRH is present in nearly a quarter of patients with vasodilatory shock and is associated with long-term odds of death that is 1.7-fold higher than that in patients with VSH. Our finding of more than 60% risk of death associated with VRH is comparable to other studies that have reported mortality rates between 40% and 80% in patients requiring high-dose vasopressor therapy (19). Vasopressor-resistant hypotension was also associated with higher severity of illness and greater organ dysfunction and significant complications such as development of severe AKI and use of kidney replacement therapy, severe fluid overload, use of mechanical ventilation, and increased ICU length of stay. We also found that patients with VRH had higher organ dysfunction at baseline compared with VSH, suggesting that organ failure may have preceded vasopressor resistance. However, it is also possible that prolonged shock before vasopressor initiation and refractory shock after vasopressor treatment may have contributed to worsening of organ failure and death.

Norepinephrine has been compared with either dopamine or epinephrine in large clinical trials showing similar or improved clinical outcomes and fewer arrhythmias (1,12). However, no vasopressor has been shown to be superior to norepinephrine for lowering the risk of death (1,12,13). The consensus view is that norepinephrine should be the recommended first-line vasopressor for most critically ill patients with vasodilatory shock (20). Although the maximum effective dose of norepinephrine remains uncertain, vasopressor responsiveness seems to decline at norepinephrine doses (4) greater than 0.5 mg/kg per minute and very high

TABLE 3. **Association of VRH and risk-adjusted 1-year mortality**

Characteristics	Unadjusted (95% CI)	*P*	Adjusted* (95% CI)	*P*
VRH vs. VSH (ref)	3.43 (3.00–3.91)	<0.001	2.93 (2.52–3.40)	<0.001
Age	1.02 (1.02–1.03)	<0.001	1.02 (1.01–1.02)	<0.001
Female vs. male (ref)	1.16 (1.04–1.30)	<0.01	1.19 (1.05–1.35)	0.01
Race				
African American vs. White (ref)	1.4 (1.12–1.75)	<0.01	1.18 (0.91–1.53)	0.22
Other	0.71 (0.50–1.01)	0.05	0.69 (0.45–1.06)	0.3
Unknown	2.15 (1.81–2.56)	<0.001	1.91 (1.56–2.34)	<0.001
APACHE III score	1.01 (1.01–1.01)	<0.001	1.01 (1.00–1.01)	<0.001
Charlson score				
1–2	1.12 (0.92–1.37)	0.2	1.03 (0.81–1.33)	0.8
3–4	1.56 (1.30–1.89)	<0.001	1.31 (0.98–1.73)	0.07
≥5	2.5 (2.07–3.03)	<0.001	2.34 (1.71–3.22)	<0.001
History of hypertension	1.17 (1.04–1.31)	0.01	0.79 (0.67–0.93)	0.004
History of diabetes	1.22 (1.07–1.40)	0.003	0.99 (0.82–1.19)	0.9
Cumulative fluid balance	1.00 (1.00–1.00)	<0.001	1.00 (1.00–1.00)	<0.001
Time from ICU admission to initiation of vasopressor	1.00 (1.00–1.00)	<0.001	1.00 (1.00–1.00)	<0.001
Admission for liver transplantation	0.19 (0.14–0.25)	<0.001	0.19 (0.13–0.26)	<0.001
Mechanical ventilation	0.76 (0.67–0.87)	<0.001	0.87 (0.74–1.01)	0.06
Median MAP	0.97 (0.97–0.98)	<0.001	0.99 (0.98–0.99)	0.001
Surgical admission	0.37 (0.33–0.42)	<0.001	0.45 (0.39–0.51)	<0.001

*Models were fitted among 5,313 patients with complete data and adjusted for covariates shown in the table. Hosmer-Lemeshow goodness-of-fit C statistic, 0.17 (area under the receiver operating characteristic curve = 0.79; 95% CI, 0.77–0.80).

TABLE 4. **Association of combination vasopressor versus monotherapy on mortality**

Characteristics	No. died/no. at risk	Unadjusted OR (95% CI)	*P*	aOR* (95% CI)	*P*
1 vasopressor (reference)	1,572/2,355				
2 vs. 1 vasopressor	522/618	1.3 (1.10–1.45)	<0.001	0.91 (0.78–1.06)	0.2
≥3 vs. 1 vasopressor	142/104	2.5 (1.58–2.66)	<0.001	0.93 (0.68–1.27)	0.6

*Models were fitted on 5,313 patients with complete data and adjusted for differences in age, sex, race, Charlson comorbidity score, history of hypertension, use of mechanical ventilation, APACHE III score, AKI severity within 7 days of ICU admission, median dose of norepinephrine equivalent dose, and median MAP in the first 6 h. Hosmer-Lemeshow goodness-of-fit C statistic, 0.12 (area under the receiver operating characteristic curve = 0.74; 95% CI, 0.73–0.76).

norepinephrine doses but can increase vascular tone and MAP in selected patients, the potential for toxicity remains a concern.

Vasopressor combination is frequently used in the treatment of vasodilatory shock as lower doses of different vasopressors are thought to have synergistic effects on vasomotor tone and reduced likelihood of toxicity compared with high-dose vasopressor monotherapy. Current guidelines also suggest a vasopressor "toolbox" approach to optimize vasomotor tone and hemodynamics in vasodilatory shock (5). However, our study shows that although combination vasopressor may help to achieve hemodynamic goals, it is not associated with lower risk of death when compared with monotherapy.

We found four unique patient clusters with varying vasopressor combination and survival that were independent of vasopressor dose and baseline severity of illness. Specifically, cluster 3 patients were younger, were more severely ill, had higher dose of norepinephrine use, and yet encountered higher risk-adjusted death than other clusters. Importantly, this higher risk of death was independent of demographics, severity of illness, and norepinephrine dose, suggesting that other patient characteristics may be associated with poor outcomes in vasodilatory shock. Recent studies in patient with cardiogenic shock and in sepsis have identified subphenotypes that have distinct outcomes (8,21).

Several studies have also found an association between candidate genotype, biomarkers and vasopressor response, and outcomes in vasodilatory shock. For example, genetic polymorphisms in the encoding *ARDβ*$_2$ have been found to be associated with a higher norepinephrine requirement; greater renal, hematologic, hepatic, and neurologic dysfunction; and an increased mortality in septic shock (6). Similarly, variants in AGTRAP have been associated with reduced MAP, lower vascular tone, and an increase in mortality (7). Interestingly, polymorphisms in *LNPEP* (leucyl and cystinyl aminopeptidase) gene, also known as vasopressinase gene, have also been associated with increased clearance of plasma vasopressin and increased mortality (22). Higher circulating concentrations of angiopoietin-2, renin, and vasopressin are also associated with severe shock, variable hemodynamic response, and increased mortality (23–25). However, genetic and biomarker testing requires further research and is currently not recommended for patients with vasodilatory shock.

Our findings have implications for conduct of clinical trials. Although our patient phenotypes need to be validated in an external cohort, our findings allow for risk stratification of patients in future clinical trials of vasodilatory shock. The inability of randomized trials in vasodilatory shock to demonstrate significant differences in clinical outcomes, despite improvement in hemodynamic markers and vasopressors, suggests heterogeneity of patient population as a potential confounder. In our study, patients in clusters 1, 2, and 4 had lower long-term risk of death compared with cluster 3. Enrolling patients in clusters 1, 2, and 4 in clinical trials examining new vasopressor therapy to reduce risk of death is likely to bias the trial toward the null. Previous studies in sepsis have shown clinical phenotypes within large, randomized trials derive harm or benefit from an intervention, which may be

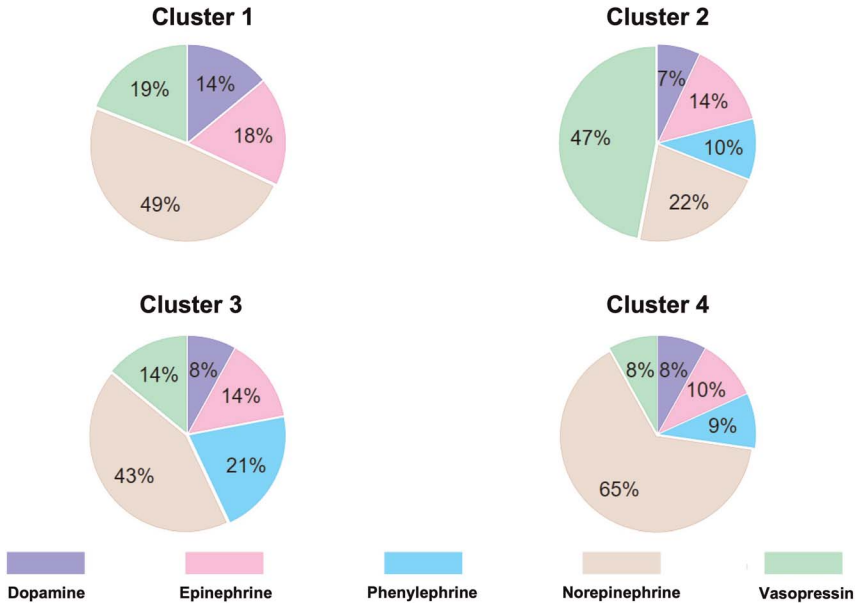

FIG. 4. **Distribution of vasopressor use by patient clusters.** Figure showing distribution of vasopressor use across different patient clusters.

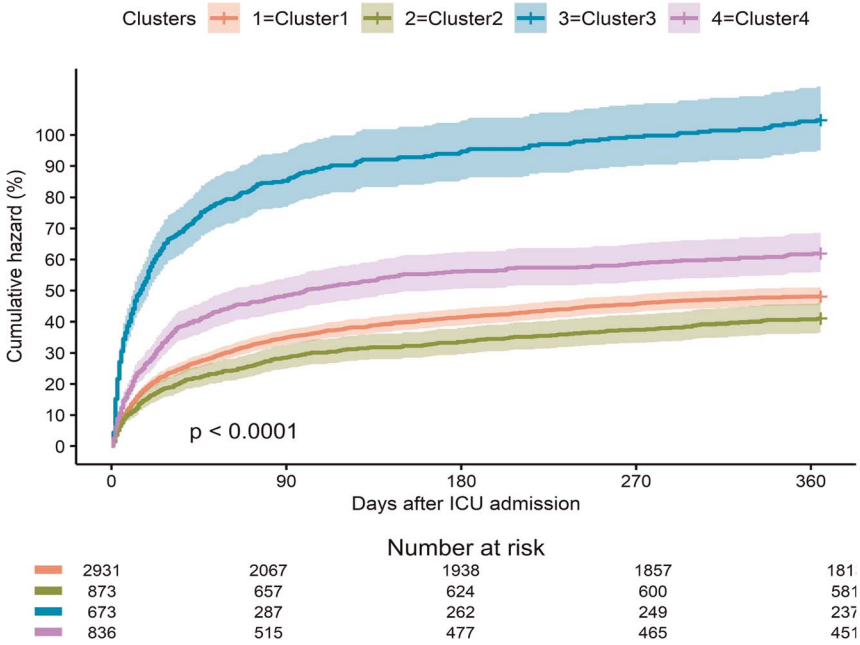

FIG. 5. **Association of patient clusters with mortality**. Kaplan-Meier failure plots showing association of patient clusters with crude 1-year mortality. Red line represents cluster 1; green line represents cluster 2; light blue line represents cluster 3; and purple line represents cluster 4. Shading represents 95% CI. Compared with patients in cluster 1, patients in clusters 3 and 4 had higher risk of death with highest risk of death in cluster 3 (log-rank $P < 0.001$).

opposite from the larger population when all patients are grouped together (21). Because 97.7% of our patients had septic shock, our findings are consistent with prior sepsis phenotype studies.

Strengths of our study include a large cohort of patient population with vasodilatory shock and characterization of long-term outcomes. We were able to account for various physiological variables such as hemodynamics in our models. Our study also has several limitations. First, being an observational study, our findings of association between VRH and patient clusters with outcomes do not imply causality. Second, we used an older data set of critically ill patient population who were admitted between 2000 and 2008. Vasopressor therapy has evolved since this time, with several new vasopressors being available. Thus, our findings may not completely apply to more recent population with vasodilatory shock. Third, we did not examine candidate biomarkers or genotypes associated with phenotypes. Fourth, most patients had septic shock, and we did not examine the type of sepsis that might have influenced the outcomes. For instance, patients with milder forms of septic shock (e.g., urosepsis) might have had different outcomes compared with intraperitoneal sepsis (e.g., perforated viscus). Fifth, our findings of shock phenotype require further validation in an external and more recent data set of critically ill patients with vasodilatory shock before clinical utilization for risk stratification and treatment.

CONCLUSION

Among critically ill patients with vasodilatory shock, VRH compared with VSH is associated with increased resource utilization and long-term risk of death. However, combination vasopressor therapy did not lower this risk of death compared with monotherapy. We identified four unique patient phenotypes that varied in patient characteristics, vasopressor type and dose, and long-term outcomes, which have implications for enrollment of patients in clinical trials of vasodilatory shock. Future studies are needed to validate these phenotypes as they relate to prognosis and optimal tailoring of vasopressor treatment.

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TABLE 5. **Association of patient cluster with risk-adjusted mortality**

Characteristics	No. died/no. at risk	Unadjusted OR (95% CI)	*P*	aOR* (95% CI)	*P*
Cluster 1 (ref)	1,119/1,812				
Cluster 2	294/579	0.82 (0.70–0.96)	0.02	0.96 (0.81–1.14)	0.6
Cluster 3	437/236	2.99 (2.51–3.57)	<0.001	2.17 (1.77–2.65)	<0.001
Cluster 4	386/450	1.39 (1.19–1.62)	<0.001	1.40 (1.18–1.66)	<0.001

*Models were fitted among 5,313 patients with complete data and were adjusted for age, sex, race, dose of norepinephrine equivalents, APACHE III score, and cumulative fluid balance. Hosmer-Lemeshow goodness-of-fit C statistic, 0.07 (area under the receiver operating characteristic curve = 0.74; 95% CI, 0.72–0.75).

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