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ORIGINAL RESEARCH

Efficacy of using early multimodal vasopressor therapy on survival after septic shock in patients receiving high-dose norepinephrine: a retrospective study based on the MIMIC database

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Abstract

Early multimodal vasopressor therapy was proposed recently to treat septic shock. However, the association between multimodal vasopressor therapy initiation timing and survival was not determined. This study aimed to investigate the association between early multimodal vasopressor therapy and survival in septic shock patients necessitating high dose norepinephrine. We conducted a retrospective single-center study of septic shock patients receiving norepinephrine as the first-line vasopressor at a maximum norepinephrine-equivalent dose >0.2 μg/kg/min. When the second vasopressor was initiated, patients were divided into three groups based on norepinephrine dosage. The primary outcome was 28-day mortality. Secondary endpoints included 90-day mortality, intensive care unit (ICU) and hospital mortality, and length of ICU and hospital stays. This study included 966 patients receiving a maximum norepinephrine-equivalent dose >0.2 μg/kg/min. Among them, 299 received an additional vasopressor when norepinephrine dose ≤ 0.2 μg/kg/min (early multimodal vasopressor therapy, EMMVT), 511 received an additional vasopressor when norepinephrine dose was between 0.2–0.5 μg/kg/min (later multimodal vasopressor therapy, LMMVT), and 156 received an additional vasopressor when norepinephrine dose ≥ 0.5 μg/kg/min (delayed multimodal vasopressor therapy, DMMVT). Age, admission type, sequential organ failure assessment (SOFA) score, metastatic cancer, liver diseases and obesity were associated with 28-day mortality. A significantly lower rate of 28-day, 90-day, ICU and hospital mortality was observed in the EMMVT group ($p < 0.001$ for all). In contrast to EMMVT, LMMVT (hazard ratio: 1.643, $p < 0.001$) and DMMVT (hazard ratio: 2.192, $p < 0.001$) were associated with an increased risk of 28-day mortality after adjusting for confounding factors. Multimodal vasopressor groups and SOFA did not interact statistically. Septic shock patients receiving norepinephrine as the first-line vasopressor and reaching a maximum norepinephrine-equivalent dose >0.2 μg/kg/min benefited from early multimodal vasopressor therapy with improved 28-day mortality, regardless of illness severity.

Keywords

Septic shock; Norepinephrine; Early multimodal vasopressor therapy; Vasopressor

1. Introduction

Septic shock is the most severe form of sepsis and is described as persistent hypotension requiring vasopressors to maintain a mean arterial pressure (MAP) of 65 mmHg despite adequate volume resuscitation. The risk of death increases by 5.3% for every hour that vasopressor initiation is delayed, similar to the time-dependent risk of delayed antimicrobials in sepsis [1, 2]. The Surviving Sepsis Campaign recommends including vasopressor initiation in the crucial 1-h bundle for fluid-resistant hypotension, with norepinephrine recommended as a first-line vasopressor [3]. The in-hospital mortality rate of patients with septic shock is higher when vasopressors are delayed [4]. Vasopressor initiation is delayed beyond 4 hours with a four-fold increase in the odds of worsening organ failure (odds ratio (OR) 4.34, 95% confidence interval (CI) 1.47–12.79, $p = 0.008$) than those who receive vasopressors within 4 hours [5]. Hence, timely vasopressors initiation is crucial for effective septic shock management.

Septic shock requiring high norepinephrine levels result in impaired catecholamine responsiveness and uncontrolled vasoplegia due to receptor signaling changes, metabolic de-

rangements and depletion of endogenous vasoactive hormones [6]. Excess norepinephrine stimulation may result in ischemic digits, splanchnic hypoxia, necrosis and serious morbidity. A mortality rate of 60% to 80% was shown in septic shock patients receiving 1 g/kg/min of norepinephrine equivalent [7, 8]. Based on a retrospective study of 324 septic shock patients, the average death rate was 48%, while mortality reached 90% for patients receiving more than 1 μg/kg/min of norepinephrine [9].

When escalated norepinephrine dosage failed to maintain MAP targets in some patients, other vasopressors were initiated. Extremely high doses of norepinephrine may induce a relative catecholamine-refractory state, which can be treated with additional vasopressors with different receptors to maintain adequate perfusion pressures and mitigate progressive multiorgan failure [2, 10]. In patients who require high vasopressor doses, it is physiologically rational to combine multiple vasopressors as part of multimodal therapy targeting multiple receptor [6]. However, the optimal norepinephrine dosage at which additional vasopressors are initiated remains unknown [11]. Septic shock patients given additional vasopressin at $<$15 μg/min norepinephrine during the Vasopressin and Septic Shock Trial (VASST) had lower 28-day and 90-day mortality [12]. Researchers found that for every 10 μg/min increase in the norepinephrine-equivalent dose at the time of vasopressin initiation in septic shock patients, the odds of in-hospital mortality increased by 20.7% [13].

Early initiation of a vasopressor is clearly better than later initiation, but the optimal timing of a secondary agent is less clear. Therefore, this study examined the association between timing of multimodal vasopressor therapy and clinical outcomes in septic shock patients receiving a maximum norepinephrine-equivalent dose of $>$0.2 μg/kg/min therapy. In high-dose vasopressor-dependent patients with septic shock, earlier initiation of multimodal vasopressor therapy was hypothesized to improve prognosis.

2. Methods

2.1 Data extraction

Data for this study were sourced from a publicly available ICU database named Medical Information Mart for Intensive Care III (MIMIC-III, version 1.4), which contains the clinical information of more than 40,000 patients admitted to the Beth Israel Deaconess Medical Center (Boston, MA, USA) [14]. After completing the "Protecting Human Research Participants" course, we were granted access to the Institutional Review Boards of the Massachusetts Institute of Technology (Cambridge, MA, USA) and Beth Israel Deaconess Medical Center. Data was extracted with a structured query language with pgAdmin4 PostgreSQL 9.6 and managed by Navicat Premium 12 (PremiumSoft CyberTech Limited company, Hongkong, China).

2.2 Study population and definitions

In 57,328 non-repetitive ICU admissions, sepsis was diagnosed according to the Angus criteria [15]. Septic shock patients receiving multiple vasopressors during ICU stay were included. Clinical vasopressors include norepinephrine, epinephrine, dopamine, phenylephrine and vasopressin. We calculated norepinephrine-equivalent vasopressor doses for epinephrine, dopamine, phenylephrine and vasopressin as previously described [16]. Since norepinephrine is recommended as first-line therapy in septic shock [3], patients given other vasopressors prior to norepinephrine or without norepinephrine usage were excluded. Septic shock patients receiving a maximum norepinephrine-equivalent dose of less than 0.2 μg/kg/min were also excluded. Finally, 966 patients included in this study were divided into three groups: (1) Early multimodal vasopressor therapy (EMMVT) group (additional vasopressors administered when norepinephrine dose $\leq$0.2 μg/kg/min); (2) Later multimodal vasopressor therapy (LMMVT) group (additional vasopressors administered when norepinephrine between 0.2–0.5 μg/kg/min); (3) Delayed multimodal vasopressor therapy (DMMVT) group (additional vasopressors administered when norepinephrine dose $\geq$0.5 μg/kg/min) (Fig. 1). A cutoff of 0.2 and 0.5 μg/kg/min was used since over 0.2 μg/kg/min of norepinephrine was previously defined as high-dose vasopressor [17]. Norepinephrine requirement more than 0.5 μg/kg/min was defined as refractory shock [18].

The following data were extracted: patients' baseline characteristics, including sex, age, admission type, comorbidity, support therapies on admission (including mechanical ventilation and renal replacement therapy), Sequential Organ Failure Assessment (SOFA) scores, time of ICU and hospital admission and discharge, and the date of death. A 28-day mortality was the primary endpoint. 90-day mortality, ICU and hospital mortality, as well as the length of ICU and hospital stay were secondary endpoints.

2.3 Statistical analysis

Continuous variables were tested for normality using the Shapiro-Wilk test. Data with a normal distribution were presented as mean $\pm$ standard deviation (SD), while skewed variables were summarized as medians with interquartile ranges (IQR). Categorical variables were presented as frequencies and percentages. Continuous variables were compared using the *t* test or analysis of variance for normally-distributed data, and the Kruskal-Wallis test or Mann-Whitney test for skewed data. Univariate analysis was used to identify variables associated with 28-day mortality based on baseline characteristics of survivors and non-survivors. Covariates with $p < 0.05$ were entered into the Cox proportional hazard regression model to determine the association between multimodal vasopressor therapy timing and 28-day mortality. We calculated variance inflation factors for each variable in the Cox proportional hazard model to test collinearity. The best fit model was selected using stepwise regression using Akaike information criteria via both forward and backward selection.

3. Results

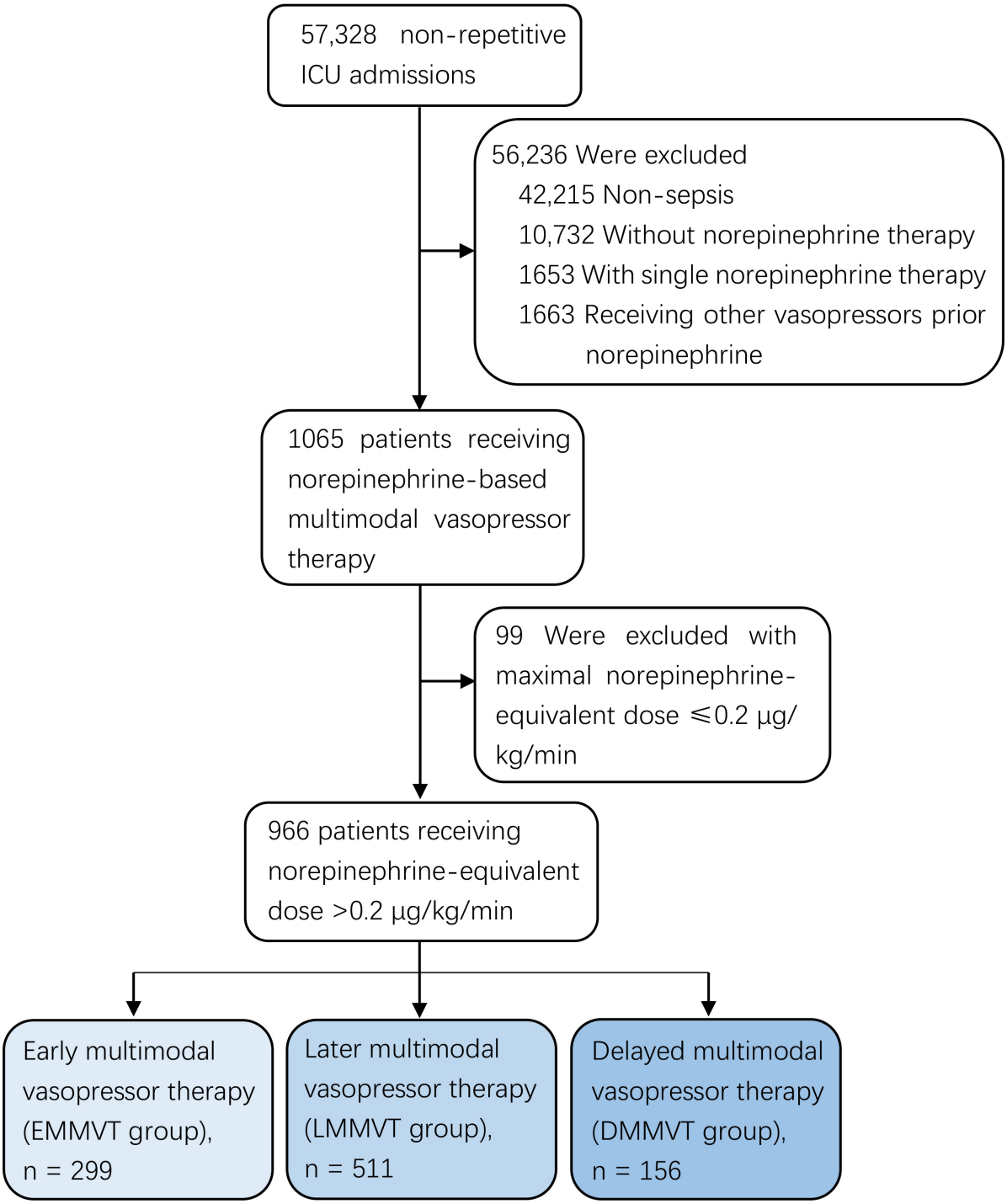

FIGURE 1. Flow diagram describing the screening, recruitment of patients. ICU: intensive care unit.

3.1 Baseline characteristics

This study included 966 patients who received a maximum norepinephrine-equivalent dose of >0.2 μg/kg/min (Fig. 1). Among them, 299 received an additional vasopressor when norepinephrine dose was less than 0.2 μg/kg/min (EMMVT), 511 received an additional vasopressor when norepinephrine dose was between 0.2–0.5 μg/kg/min, while 156 received an additional vasopressor when norepinephrine dose was more than 0.5 μg/kg/min. Survivors were younger than non-survivors, and age was significantly associated with 28-day mortality ($p < 0.001$, Table 1). More non-survivors were admitted to the ICU in emergency or urgent situations, indicating unplanned medical care. Comorbidities, including metastatic cancer ($p < 0.001$), liver diseases ($p = 0.002$) and obesity ($p = 0.004$), were significantly associated with 28-day mortality. The utilization of mechanical ventilation and renal replacement therapy was comparable between survivors and non-survivors ($p = 0.749$ and $p = 0.080$, respectively). Septic shock patients had a median SOFA score of 10. Higher SOFA scores significantly increased the risk of 28-day death ($p < 0.001$). SOFA scores for liver, kidney, and coagulation were significantly higher among non-survivors (Table 1). Baseline characteristics according to the EMMVT, LMMVT and DMMVT group was shown in **Supplementary Table 1**.

TABLE 1. Baseline characteristics of study population according to 28-day survival.

Characteristics	Total (n = 966)	Survivor (n = 417)	Non-survivo (n = 549)	*p* value
Male gender (n, %)	540 (55.9)	234 (56.1)	306 (55.7)	0.959
Age (yr, n, %)				
18–50	175 (18.1)	106 (25.4)	69 (12.6)	
50–60	172 (17.8)	75 (18.0)	97 (17.7)	
60–70	202 (20.9)	82 (19.7)	120 (21.9)	<0.001
70–80	211 (21.8)	93 (22.3)	118 (21.5)	
>80	206 (21.3)	61 (14.6)	145 (26.4)	
Admission type				
Elective	47 (4.9)	31 (7.4)	16 (2.9)	
Emergency	897 (92.9)	379 (90.9)	518 (94.4)	0.003
Urgent	22 (2.3)	7 (1.7)	15 (2.7)	
Comorbidity				
Congestive heart failure	296 (30.6)	120 (28.8)	176 (32.1)	0.305
Hypertension	158 (16.4)	66 (15.8)	92 (16.8)	0.765
Diabetes mellitus	292 (30.2)	122 (29.3)	170 (31.0)	0.616
Renal failure	198 (20.5)	80 (19.2)	118 (21.5)	0.424
Metastatic cancer	60 (6.2)	11 (2.6)	49 (8.9)	<0.001
Chronic pulmonary disease	178 (18.4)	79 (18.9)	99 (18.0)	0.781
Cardiac arrhythmia	304 (31.5)	129 (30.9)	175 (31.9)	0.809
Liver diseases	123 (12.7)	37 (8.9)	86 (15.7)	0.002
Obesity	62 (6.4)	38 (9.1)	24 (4.4)	0.004
Support therapy				
Mechanical ventilation	789 (81.7)	343 (82.3)	446 (81.2)	0.749
Renal replacement therapy	124 (12.8)	44 (10.6)	80 (14.6)	0.080
SOFA score	10 (8–13)	9 (7–11)	11 (8–14)	<0.001
SOFA score for each organ				
Cardiovascular	4 (4–4)	4 (4–4)	4 (4–4)	0.107
Respiration	3 (0–4)	3 (0–3)	3 (0–4)	0.076
Liver	0 (0–2)	0 (0–1)	0 (0–2)	<0.001
CNS	0 (0–1)	0 (0–1)	0 (0–1)	0.165
Renal	2 (1– 4)	1 (0–3)	3 (1–4)	<0.001
Coagulation	1 (0–2)	0 (0–2)	1 (0–2)	0.001
Positive blood culture	563 (58.3)	243 (58.3)	320 (58.3)	1.000

SOFA: sequential organ failure assessment; CNS: central nervous system.

Regarding the timing of multimodal vasopressor therapy, the norepinephrine rate at which an additional vasopressor was initiated was evaluated. Survivors received significantly earlier multimodal vasopressor therapy than non-survivors (median norepinephrine rate: 0.2 μg/kg/min *vs.* 0.3 μg/kg/min, $p < 0.001$) (Fig. 2A). Non-survivors received more vasopressor types (Fig. 2B). Among second-line vasopressors, vasopressin ranked highest (36.7%), followed by phenylephrine (35.0%), dopamine (16.6%) and epinephrine (3.6%) (**Supplementary Table 2**). The times of the second vasopressor after septic shock onset were calculated. The median time of the second vasopressor given were 5 mins, 116 mins and 38 mins in EMMVT, LMMVT and DMMVT groups, respectively (**Supplementary Fig. 1**).

3.2 Primary analysis

A survival curve analysis was performed to investigate the association between multimodal vasopressor timing and 28-day mortality. LMMVT (hazard ratio, 1.849; $p < 0.001$) and DMMVT (hazard ratio, 2.329; $p < 0.001$) were significantly correlated with 28-day mortality (Fig. 2C). Additionally, we included age, admission type, comorbidities, SOFA score and

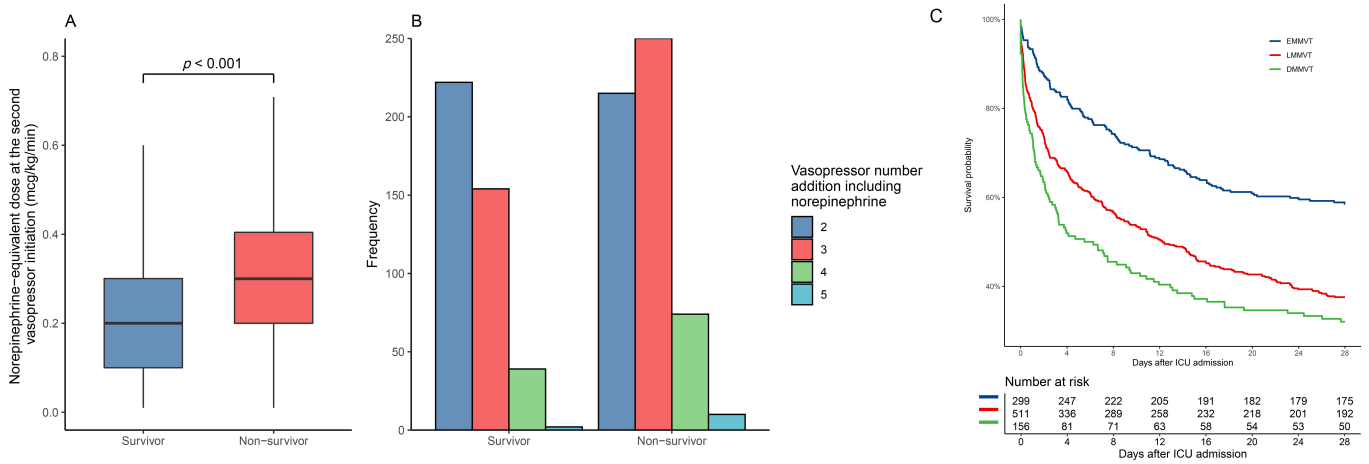

FIGURE 2. Comparisons of clinical outcomes and vasopressor usage between survivors and non-survivors. (A) Norepinephrine dose at the second vasopressor initiation between 28-day survivors and non-survivors. Outliers were not presented in boxplot. (B) Numbers of vasopressors used among survivors and non-survivors. Vasopressors including norepinephrine, epinephrine, dopamine, phenylephrine and vasopressin were considered. (C) Kaplan-Meier curves showing the association between the multimodal vasopressor therapy timing and the 28-day mortality. EMMVT: early multimodal vasopressor therapy; LMMVT: later multimodal vasopressor therapy; DMMVT: delayed multimodal vasopressor therapy; ICU: intensive care unit.

multimodal vasopressor therapy in a multivariable Cox proportional hazard model. Compared to EMMVT, LMMVT (hazard ratio, 1.643; $p < 0.001$) and DMMVT (hazard ratio, 2.192; $p < 0.001$) were associated with increased risk of 28-day mortality (Table 2). Several other covariates were significantly associated with 28-day mortality, including older age, emergency and urgent admission, SOFA score, metastatic cancer, and liver diseases. However, obesity was a protective factor (Table 2).

A second model included the interaction between multimodal vasopressor groups and SOFA categories, since we hypothesized that the effect of multimodal vasopressor time on survival might differ depending on illness severity. Patients were stratified according to SOFA score quartiles. For patients with SOFA score <8 ($p < 0.001$), SOFA score 10–13 (0.006) and SOFA score >13 (0.030), later or delayed multimodal vasopressor therapy was associated 28-day mortality (**Supplementary Fig. 2**). There was no association between the multimodal vasopressor timing and the 28-day mortality among patients with SOFA of 8–10 scores. In the second model, the interaction between multimodal vasopressor groups and SOFA were not statistically significant (**Supplementary Table 3**).

3.3 Outcome comparisons

The clinical outcomes were compared between the EMMVT, LMMVT and DMMVT groups (Table 3). Patients receiving delayed or late multimodal vasopressor therapy had higher 28-day, 90-day, ICU and hospital mortality rate ($p < 0.001$ for all). However, both LMMVT and DMMVT groups had significantly longer ICU and hospital stay ($p < 0.001$ for both) than the EMMVT group. With the delay of multimodal vasopressor therapy, the maximal norepinephrine dosage increased and alive days significantly decreased. However, ICU readmission was not associated with the multimodal vasopressor timing.

Even though norepinephrine, epinephrine, phenylephrine and dopamine share a different receptor activity, they are all catecholamine derivatives. A lower maximum dose of norepinephrine was employed when vasopressin was used as the second-line vasopressor, compared with catecholamine (**Supplementary Table 4**). In both catecholamine (including epinephrine, phenylephrine and dopamine) and vasopressin group, early use of another vasopressor improved 28-day mortality (**Supplementary Fig. 3**). Catecholamine and vasopressin, however, did not differ significantly.

4. Discussion

Septic shock is defined as persistent sepsis-induced hypotension despite adequate fluid resuscitation. Optimizing fluid resuscitation is the first step before initiation of vasopressor support, according to guidelines. Sepsis patients with a positive fluid balance have a higher mortality rate [19]. There is a growing body of evidence to recommend early initiation of norepinephrine therapy [20, 21], which is significantly associated with a lower amount of resuscitation fluids, less fluid accumulation, lower incidences of cardiogenic pulmonary edema and new-onset arrhythmia, increased shock control and improved mortality [20–22]. For patients with refractory shock, increasingly high doses of norepinephrine are needed to maintain the MAP target. Although high doses of norepinephrine therapy are associated with worse clinical outcomes, there is no high-quality evidence to recommend the use of other vasopressors over norepinephrine. Vasopressin is recommended as a secondary vasopressor for septic shock. Compared with norepinephrine, low-dose vasopressin did not reduce mortality rates in patients with septic shock in the VASST trial [12]. Vasopressin, however, significantly reduced the use of renal replacement therapy and improved renal function more than norepinephrine [23–25].

However, the optimal timing of administration of the

TABLE 2. Cox proportional hazard models exploring the association between the time of multimodal vasopressor and 28-day mortality.

Factors	Hazard ratio	95% CI	*p* value
Age (yr, n, %)			
18–50	Reference	Reference	Reference
50–60	1.679	1.231–2.289	0.001
60–70	1.947	1.442–2.628	<0.001
70–80	2.054	1.515–2.785	<0.001
>80	2.966	2.206–3.987	<0.001
Admission type			
Elective	Reference	Reference	Reference
Emergency	1.755	1.065–2.890	0.027
Urgent	2.308	1.138–4.682	0.020
Metastatic cancer	2.365	1.754–3.191	<0.001
Liver diseases	1.405	1.096–1.800	0.007
Obesity	0.620	0.410–0.939	0.024
SOFA score	1.106	1.081–1.133	<0.001
Multimodal vasopressor therapy			
EMMVT	Reference	Reference	Reference
LMMVT	1.643	1.331–2.028	<0.001
DMMVT	2.192	1.684–2.852	<0.001

SOFA: sequential organ failure assessment; CI: Confidence interval; EMMVT: early multimodal vasopressor therapy; LMMVT: later multimodal vasopressor therapy; DMMVT: delayed multimodal vasopressor therapy.

TABLE 3. Clinical outcomes of 966 septic shock patients according to time of multimodal vasopressor therapy.

Outcomes	Total (n = 966)	EMMVT (n = 299)	LMMVT (n = 511)	DMMVT (n = 156)	*p* value
Mortality (n, %)					
28-day	549 (56.8)	124 (41.5)	319 (62.4)	106 (67.9)	<0.001
90-day	613 (63.5)	150 (50.2)	353 (69.1)	110 (70.5)	<0.001
ICU	531 (55.0)	122 (40.8)	305 (59.7)	104 (66.7)	<0.001
Hospital	553 (57.2)	129 (43.1)	319 (62.4)	105 (67.3)	<0.001
Length of stay (median days, IQR)					
ICU	7.20 (2.65–14.82)	8.95 (4.26–16.80)	6.29 (2.29–14.52)	4.32 (1.45–11.85)	<0.001
Hospital	11.46 (3.48–22.22)	14.34 (7.77–28.34)	10.50 (3.04–21.17)	7.63 (1.42–19.46)	<0.001
Other outcomes (median with IQR or number with percent)					
Maximal norepinephrine dose (μg/kg/min)	0.401 (0.280–0.513)	0.250 (0.171–0.495)	0.400 (0.300–0.501)	0.549 (0.501–1.000)	<0.001
Days alive at 28 days	15.4 (2.1–28)	28 (7.3–28)	12.3 (1.8–28)	5.9 (0.8–28)	<0.001
Ventilation-free days at 28 days[a]	20.4 (12.4–25.0)	20.5 (12.0–25.2)	20.4 (13.3–25.2)	19.0 (11.3–23.9)	0.597
Acute kidney injury during ICU stay	213 (22.0)	57 (19.1)	116 (22.7)	40 (25.6)	0.241
Readmission to ICU	56 (5.8)	20 (6.7)	28 (5.5)	8 (5.1)	0.720

[a] *Ventilation-free days were calculated at day 28 and was defined as the number of days the patient was alive (starting on the day of admission in ICU) and free of mechanical ventilation.*

EMMVT: early multimodal vasopressor therapy; LMMVT: later multimodal vasopressor therapy; DMMVT: delayed multimodal vasopressor therapy; ICU: intensive care unit; IQR: interquartile range.

secondary agent remains unclear. Recent retrospective study reported that arginine vasopressin initiation at a norepinephrine equivalent of >40 μg/min was associated with non-responsiveness to arginine vasopressin, which increased the risk of death in septic shock patients [26]. An observational study also demonstrated that the risk of in-hospital mortality increased by 20.7% for every 10 μg/min increase in the norepinephrine-equivalent dose up to 60 μg/min at the time of vasopressin initiation, but no association was observed when norepinephrine-equivalent dose exceeded 60 μg/min [13]. These findings suggest that the initiation of multimodal vasopressor therapy is associated with the improved clinical outcomes. Thus, similar to the use of broad-spectrum antimicrobials in sepsis, an early multimodal vasopressor strategy, also termed "broad-spectrum vasopressors" was proposed recently [2, 11]. Norepinephrine is the recommended first-line vasoactive drug, whereas epinephrine, phenylephrine dopamine, and vasopressin are usually considered second-line agents [3]. Despite being catecholamines, norepinephrine, epinephrine, phenylephrine and have different receptor activities [27]. From this perspective, using a norepinephrine and another type of catecholamine as a second-line vasopressor might also be "multimodal". This study categorized the initiation of the second agent based on the norepinephrine dose. In septic shock patients receiving a maximum norepinephrine-equivalent dose >0.2 μg/kg/min, the earlier the multimodal vasopressors are initiated, the better prognosis, regardless of the agent type (catecholamine or vasopressin). Since high-dose norepinephrine therapy often results in adverse effects and is associated with poor outcomes in septic shock [28, 29], norepinephrine-sparing approaches are praised [11, 30]. This study found the EMMVT group received a significantly lower norepinephrine dose, indicating that early and broad-spectrum vasopressors reduced norepinephrine use, thus preventing toxic side effects from high-dose norepinephrine. In addition, it seemed that the usage of more types of vasopressors was associated with higher mortality (Fig. 2). Possibly, the worse hemodynamic instability facilitates the use of more vasopressors, resulting in a higher mortality.

In this study, the interaction between illness severity and multimodal vasopressor timing was also analyzed in the multivariable models. However, the interaction was not significant, indicating that the early multimodal vasopressor strategy was beneficial for patients with septic shock, regardless of illness severity. According to Guerci *et al.* [31], adding an early adjunct vasopressor to norepinephrine might not be necessary for "controlled shock", in contrast to refractory shock. Future studies should also focus on efforts to individualize the use of vasopressors, considering the patient's pathophysiological characteristics.

This study has some limitations. First, given the single-center retrospective nature of the study, the results obtained herein need to be confirmed in a well-designed prospective multicenter cohort before any extrapolation can be made. Second, although we demonstrated that early multimodal vasopressor therapy was beneficial for patients with septic shock, we failed to determine which vasopressor was the optimal second agent. Third, we failed to assess the timing of angiotensin II on septic shock, since no record about angiotensin II were searched in MIMIC database. Lastly, because of its retrospective nature, we failed to assess the impact of multimodal vasopressor therapy on long-term survival, as part of the patents in the MIMIC III database had date records of death only up to 90 days in the future.

5. Conclusions

For septic shock patients receiving norepinephrine as the first-line vasopressor and reaching a maximal norepinephrine-equivalent dose >0.2 μg/kg/min, early multimodal vasopressor therapy was associated with improved 28-day mortality, regardless of the illness severity. Given the limitations of the present retrospective study, randomized trials will be needed to conclusively endorse early multimodal therapy.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

TTW—conceptualization and writing–original draft. XHZ—data curation, formal analysis and methodology. PHY—conceptualization, supervision and writing–review & editing. JQZ—methodology and software. QL—project administration and writing–review & editing. XLY—Methodology, software and visualization. All authors approved the final version to be submitted for publication.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Access to the MIMIC database was approved by the Institutional Review Boards of the Massachusetts Institute of Technology (Cambridge, MA, USA) and the Beth Israel Deaconess Medical Center (NO. 2001P001699). Informed consent was waived, because all patients were de-identified and all dates in the database were shifted to protect patient confidentiality.

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Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1831947679327764480/attachment/Supplementary%20material.docx.

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