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Optimal norepinephrine-equivalent dose to initiate epinephrine in patients with septic shock

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ABSTRACT

Purpose: The specific norepinephrine dose at which epinephrine should be added in septic shock is unclear. This study sought to determine the norepinephrine-equivalent dose at epinephrine initiation that correlated with hemodynamic stability.

Methods: Septic shock patients receiving both norepinephrine and epinephrine were included in this study. Classification and regression tree analysis was conducted to determine breakpoints in norepinephrine-equivalent dose predicting hemodynamic stability, with two cohorts identified. The primary outcome was hemodynamic stability, and secondary outcomes were shock-free survival, time to achieve hemodynamic stability, and change in SOFA score.

Results: Optimal dose group was identified as initiating epinephrine when norepinephrine-equivalent dose was between 37 and 133 μg/min. A total of 138 and 61 patients were classified in optimal and non-optimal dose groups, respectively. Baseline characteristics were similar between groups except vasopressin use was more frequent in the optimal dose group. More patients in optimal dose group versus non-optimal dose group achieved hemodynamic stability (40 [29%] vs. 9 [14.8%]), absolute risk difference 14.2% [95% CI 2.5–25.9%]; $p = .03$). On multivariable analysis, initiating epinephrine within the optimal norepinephrine-equivalent dose range was independently associated with higher odds of hemodynamic response (OR 3.06 [95% CI 1.2–7.6]; $p = .02$). No differences were observed in other secondary outcomes.

Conclusions: Initiation of epinephrine when patients were receiving norepinephrine-equivalent doses of 37–133 μg/min was associated with a higher rate of hemodynamic stability.

1. Introduction

Timely initiation of appropriate therapy, including fluids, antibiotics, and vasopressors, is a critical determinant of clinical outcomes in patients with septic shock [1-3]. A delay in vasopressor initiation has been shown to increase mortality and organ failure rates [1,2]. The 2016 Surviving Sepsis Campaign guidelines recommend initiating vasopressors within 6 h in patients who do not respond to the initial fluid bolus in order to maintain mean arterial pressure (MAP) [3]. Norepinephrine is recommended as the first-line vasopressor for most patients, and the guidelines recommend the addition of either vasopressin or epinephrine as second-line options. However, there are limited data describing how and in which order additional vasopressors should be administered in patients poorly responsive to norepinephrine, leaving clinicians with little guidance on the optimal utilization of second-line vasopressors [4-7]. For this reason, the initiation of adjunctive vasoactive agents is largely driven by clinician preference or institutional protocols based on limited evidence.

While norepinephrine primarily increases systemic vascular resistance, epinephrine, in doses utilized in septic shock, increases both systemic vascular resistance and cardiac output [8,9]. Whether inotropy with epinephrine will provide additional benefit is unclear because most patients with septic shock have an elevated cardiac output after fluid resuscitation. Indeed, varied norepinephrine-equivalent dosage ranges exist in the literature for when a second vasopressor with inotropic activity was added [4-6]. Further complicating practice decisions,

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the literature supporting the guideline suggestion for adding epinephrine mostly evaluated epinephrine as first-line therapy and not as second-line therapy [3]. Due to the overall lack of guidance on when to initiate adjunctive vasoactive agents, a better understanding of ideal vasopressor use is necessary. For this reason, this study sought to define the optimal norepinephrine-equivalent dose for initiation of adjunctive epinephrine in patients with septic shock.

2. Methods

2.1. Study design

This was a non-interventional, retrospective cohort study that included patients admitted to a tertiary academic medical center between August 1, 2010 and August 31, 2016. Patients were included if they were at least 18 years old, admitted to the medical, surgical, or neurosciences intensive care unit (ICU), had septic shock, received norepinephrine as their initial vasopressor, and received epinephrine (initiated after norepinephrine) for at least one hour. Use of other vasopressors during or after norepinephrine initiation was permitted. Patients were excluded if epinephrine was initiated prior to admission to the hospital or if epinephrine was initiated before or within 30 min of norepinephrine initiation. This 30 min cutoff was utilized to help identify patients receiving epinephrine on transfer from another institution. Septic shock was defined as having a known or suspected source of infection, Sequential Organ Failure Assessment (SOFA) score of at least 2, and a serum lactate of at least 2 mmol/L [10]. Guideline-concordant antibiotics were defined as receiving antibiotics described in the Centers for Medicare and Medicaid Services sepsis measure [11]. For patients with multiple septic shock episodes within the same admission, only the first episode was considered for inclusion. This study was approved by the Cleveland Clinic Institutional Review Board.

The primary objective of the study was to identify the optimal norepinephrine-equivalent dose at which epinephrine was initiated in patients with septic shock. To accomplish this, classification and regression tree (CART) analysis was utilized to identify two patient cohorts: optimal and non-optimal norepinephrine-equivalent dose groups. CART analysis identified the dose cut-off most likely to predict hemodynamic stability. The secondary objective of the study was to compare clinical outcomes between the optimal and non-optimal dose cohorts. In an exploratory analysis, patient groups were determined based on the two CART-identified norepinephrine dose cut-offs and evaluated as three cohorts instead of two.

2.2. Study outcomes

The primary outcome was the achievement of hemodynamic stability after epinephrine initiation. Hemodynamic stability was defined as two consecutive down-titrations in vasopressor dosage requirements without a subsequent increase in dosage within eight hours [12]. All vasopressor requirements were assessed based on norepinephrine-equivalent doses [13]. Hemodynamic data and vasopressor requirements were collected at norepinephrine and epinephrine initiation, and every hour for 24 h, at 48 h, at 72 h, and at 7 days after epinephrine initiation. Secondary outcomes evaluated between the two cohorts included the time to achieving hemodynamic stability, shock-free survival, change in SOFA score 48 h after epinephrine initiation, ICU-free days during the hospital admission, and hospital length of stay [3,14]. Time to achieving hemodynamic stability was defined as the time from epinephrine initiation to the time where the patient had the first down-titration in vasopressor requirements during the episode where the patient met the hemodynamic stability endpoint. Shock-free survival was defined as the patient being alive and off all vasopressors on the seventh day after epinephrine initiation. The change in SOFA score was only evaluated for patients that did not expire within 48 h of epinephrine initiation.

Safety outcomes were evaluated over the first eight hours after epinephrine initiation and included the development of hyperglycemia, hyperlactatemia, and new-onset arrhythmias. Hyperglycemia was defined as a blood glucose level >180 mg/dL after epinephrine initiation that required the initiation of an insulin infusion [12]; patients were not evaluated for this outcome if they were already on an insulin infusion at epinephrine initiation. Hyperlactatemia was defined as an increase in serum lactate concentration by >1 mmol/L from baseline after epinephrine initiation [15]. Finally, new-onset arrhythmia was defined as an increase in heart rate to >140 beats/min after epinephrine initiation or worsening in the documented heart rhythm after initiation of epinephrine [15,16].

2.3. Statistical analysis

To determine the optimal norepinephrine-equivalent dose at epinephrine initiation associated with hemodynamic stability, a CART analysis was conducted. CART analysis is a non-parametric statistical method which uses a decision tree to solve classification and regression problem in a binary recursive partitioning manner where each group of patients are represented by a node in the decision tree that can only split into two groups. This binary partitioning process is applied over and over again until a breakpoint is identified. The CART-defined breakpoints were then used to identify the two cohorts (optimal and non-optimal norepinephrine-equivalent dose groups), and outcomes were compared between the two groups. Continuous data were analyzed with Student's *t*-test or Mann-Whitney *U* test, and categorical data were analyzed with Fisher's exact test or Chi square test, as appropriate. In the exploratory analysis, Kruskal-Wallis rank test was utilized to analyze continuous variables. For assessing time to hemodynamic stability, a survival analysis with the log-rank test was used. A univariate Cox proportional hazards model was developed, and the proportional hazards assumption was assessed with graphical assessment of log-log survival plots. Multivariable logistic regression was conducted to adjust for factors that may have confounded the effect of cohort assignment on hemodynamic stability. Variables included in the model were those thought to influence disease severity and ability to achieve hemodynamic stability. These variables were tested for multicollinearity and only one factor was included in the multivariable regression analysis if two factors showed collinearity. The CART analysis was performed using R package "rpart." All further analyses were conducted using Stata 14 (StataCorp, College Station, TX, USA). A two-sided significance level of 0.05 was used for all analyses.

3. Results

There were 803 patients screened for inclusion in the study. Of these, 536 did not meet the inclusion criteria, and 68 were subsequently excluded from the study. The most common reason patients were not included in this study was that they did not meet the study definition of septic shock. A total of 199 patients met the inclusion criteria without meeting exclusion criteria and were included in the analysis (Fig. 1). The CART analysis identified two significant breakpoints in norepinephrine-equivalent dose at epinephrine initiation associated with hemodynamic stability (Fig. 2). The first breakpoint was norepinephrine-equivalent doses greater than or equal to 133 μg/min, and the second was norepinephrine-equivalent doses <37 μg/min. Based on these findings, the optimal norepinephrine-equivalent dose cohort was defined as patients who were receiving norepinephrine-equivalent doses between 37 and 133 μg/min at epinephrine initiation ($n = 138$), and the non-optimal dose cohort was defined as those who were receiving norepinephrine-equivalent doses outside of this range at epinephrine initiation (>133 μg/min or <37 μg/min, $n = 61$). The exploratory analysis findings with three cohorts are presented in the supplementary material.

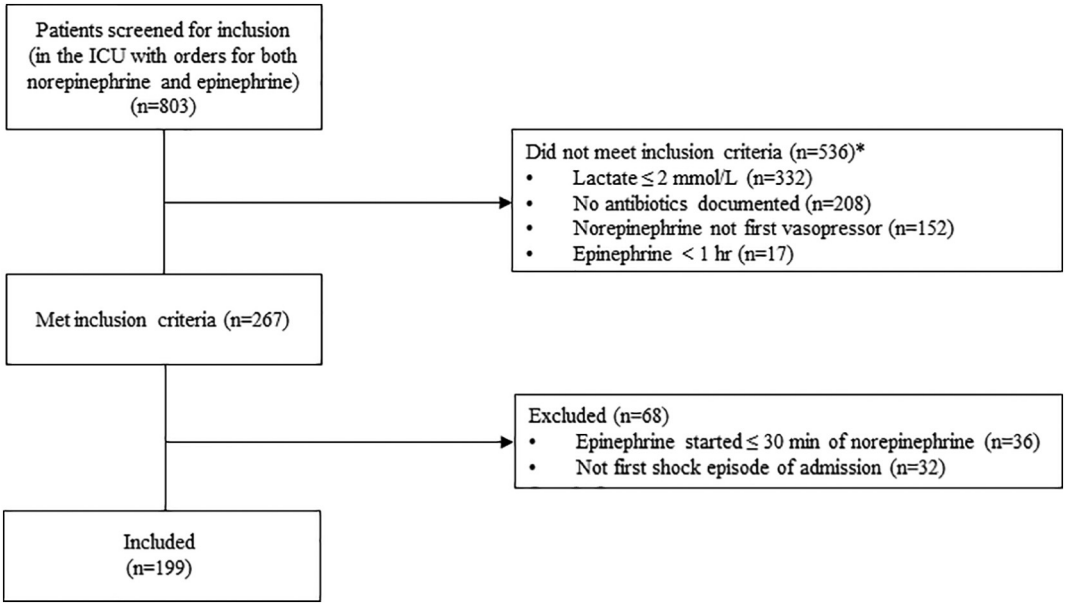

Fig. 1. Inclusion and exclusion flowchart. *ICU* intensive care unit. *Patients may have failed to meet multiple inclusion criteria.

More patients in the optimal dose group received vasopressin compared to the non-optimal dose group (115 [83.3%] vs. 38 [62.3%]; $p = .001$); otherwise, there were no significant differences in baseline characteristics between the two cohorts (Table 1). The median norepinephrine-equivalent dose at epinephrine initiation was 80 μg/min (interquartile range [IQR] 65–96.5 μg/min) in the optimal dose group. In patients with norepinephrine-equivalent doses <37 μg/min ($n = 27$), the median dose was 20 μg/min (IQR 7–30 μg/min), and the median norepinephrine-equivalent dose was 155 μg/min (IQR 145–175 μg/min) for those with doses >133 μg/min at epinephrine initiation ($n = 34$). The median SOFA score at epinephrine initiation for all patients included in the study was 12 (IQR 10–14), with no differences observed between groups. About 70% of patients received fluids in the six hours prior to the first documented norepinephrine administration, and steroids were administered to 83% of patients.

Primary and secondary outcomes are presented in Table 2. There were 40 patients (29%) in the optimal dose group and nine patients (14.8%) in the non-optimal dose group that achieved the primary outcome of hemodynamic stability (absolute risk difference 14.2% [95% CI 2.5–25.9%]; $p = .03$). In the Cox proportional hazards model, receiving norepinephrine-equivalent doses between 37 and 133 μg/min at epinephrine initiation was associated with an increased rate of achieving hemodynamic stability (HR 2.09 [95% CI 1.01–4.30]; $p = .05$), Fig. 3. After adjustment for vasopressin use, SOFA, MAP, and lactate with multivariable logistic regression, initiating epinephrine within the optimal norepinephrine-equivalent dose range was independently associated with higher odds of hemodynamic response (OR 3.06 [95% CI 1.2–7.6]; $p = .02$). There was no significant difference between groups in shock-free survival ($p = .76$) or change in SOFA score at 48 h after epinephrine initiation ($p = .08$). Mortality rates in the ICU were over 90%, and no differences were observed between groups in hospital length of stay, ICU-free days, hyperlactatemia, new arrhythmia, or hyperglycemia.

In the exploratory analysis, there were four patients (15%) in the norepinephrine-equivalent dose <37 μg/min group, 40 patients (29%) in the norepinephrine-equivalent dose 37–133 μg/min group, and five patients (15%) in the norepinephrine-equivalent dose >133 μg/min group that achieved the primary outcome of hemodynamic stability ($p = .1$), Supplemental Table 2.

4. Discussion

To our knowledge, this is the first study evaluating the optimal norepinephrine-equivalent dose for adjunctive epinephrine initiation

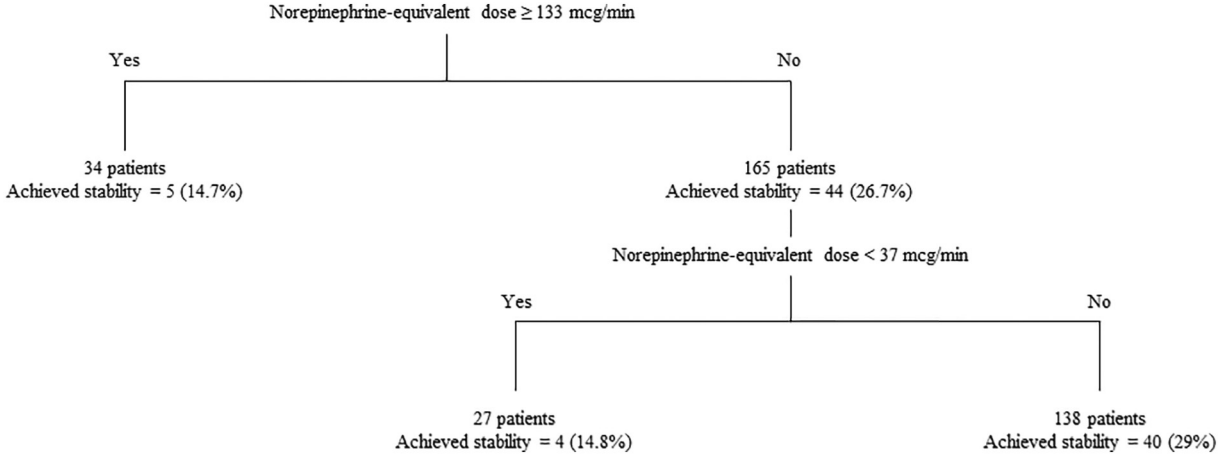

Fig. 2. Classification and regression tree analysis results.

Table 1
Baseline characteristics.

	Optimal dose group	Non-optimal dose group	*P*-value
	($n = 138$)	(n = 61)	
Epinephrine initiation dose, mcg/min	4 (1−10)	4 (1.3–10)	0.68
Vasopressin, n (%)	115 (83.3)	38 (62.3)	0.001
Age, years	60 (51–70)	60 (49–69)	0.41
Male, n (%)	74 (53.6)	36 (59)	0.48
Weight, kg	84 (71.1–106.1)	90.2 (73.4–121.1)	0.16
SOFA score	12 (9–14)	12 (10–14)	0.82
APACHE III score	103 (76–130)	92 (64.5–135.5)	0.86
MAP, mmHg	60 (55–71)	61 (56–74)	0.43
Pulse, bpm	108 (89–121)	105 (88–119.5)	0.59
CVP, mmHg[a]	11 (7–17)	12.5 (7–18)	0.76
$ScvO_2$, %[b]	61 (53–75)	64 (42–73)	0.43
Lactate, mmol/L	9.1 (4.7–13.1)	8.5 (4–16)	0.91
Intubated, n (%)	102 (73.9)	44 (72.1)	0.79
Renal replacement therapy, n (%)			0.38
CRRT	58 (42.3)	21 (34.4)	
IHD	12 (8.8)	5 (8.2)	
PD	0 (0)	1 (1.6)	
Guideline-concordant antibiotics, n (%)	130 (94.2)	60 (98.4)	0.28
Received fluids, n (%)	96 (69.6)	43 (70.5)	0.90
Fluids administered, mL	1000 (0–1500)	680 (0–1680)	0.85
Hydrocortisone equivalent dose, mg/day	200 (200−300)	200 (160–200)	0.17

Continuous data presented as median (IQR).
SOFA sequential organ failure assessment, *APACHE* acute physiology and chronic health evaluation, *MAP* mean arterial pressure, *CVP* central venous pressure, *$ScvO_2$* central venous oxygen saturation, *CRRT* continuous renal replacement therapy, *IHD* intermittent hemodialysis, *PD* peritoneal dialysis, *IQR* interquartile range.
[a] Data available in $n = 33$ and $n = 16$, respectively.
[b] Data available in $n = 78$ and $n = 26$, respectively.

in patients with septic shock who are refractory to norepinephrine. The use of CART analysis assisted in identifying two breakpoints in the norepinephrine-equivalent dose where it may be most beneficial to add epinephrine in this population. Interestingly, CART identified two dosing breakpoints, which corresponded to hemodynamic stability in an inverse U-shaped manner. This helped in defining two groups that are less likely to benefit from the initiation of epinephrine: those with norepinephrine-equivalent doses <37 μg/min and those with doses greater than or equal to 133 μg/min. Thus, this study found that initiating epinephrine when existing vasopressor requirements are between norepinephrine-equivalent doses of 37–133 μg/min correlated with improved incidence and rate of hemodynamic stability. No significant differences were found in other secondary or safety outcomes.

Even though patients who received norepinephrine equivalents doses >133 μg/min might be physiologically different from patients who received norepinephrine equivalents doses <37 μg/min, the decision to combine both cohorts was based on our finding that patients may have worse outcomes if epinephrine was initiated too soon or too late in the clinical course. The CART analysis identified norepinephrine dose breakpoints with a complex relationship, which differs from traditional pharmacologic dosing studies evaluating for a linear dose-response relationship. The exploratory analysis of comparing three different cohorts of initiating epinephrine at norepinephrine equivalents doses <37 μg/min, 37–133 μg/min, and > 133 μg/min was also performed and reveled no difference in outcomes between the cohorts (supplementary material).

The Surviving Sepsis Campaign guidelines recommend either vasopressin or epinephrine as second-line vasopressors [3]; however, few studies evaluated epinephrine as a second-line vasopressor for septic shock. A cohort study by Nguyen and colleagues sought to determine the most appropriate second-line agent for septic shock patients that were refractory to norepinephrine, but only one of the 235 patients in this study received epinephrine as a second-line agent, and this patient was excluded from the analysis [17]. The guideline recommendations for the use of epinephrine as a second-line vasopressor seem to be primarily based on evidence from two studies comparing epinephrine to norepinephrine alone or norepinephrine with dobutamine as first-line therapy for septic shock. There were no differences in effectiveness between the epinephrine and norepinephrine study arms in each of the studies, but more frequent adverse effects were reported in patients receiving epinephrine [15,16]. One randomized controlled trial evaluated the addition of epinephrine or dobutamine to norepinephrine in septic shock patients and found improvements in heart rate and MAP in patients who received epinephrine, but mortality did not differ between the two groups [18]. As such, this study adds further information on the use of epinephrine in patients' refractory to norepinephrine.

The dose that constitutes failure of norepinephrine as a first-line vasoactive agent is not well defined in literature. Additionally, the maximal norepinephrine doses used by clinicians and researchers are variable and often subjective. This study, as expected, identified a wide range of norepinephrine-equivalent doses at which initiating epinephrine correlated with improved hemodynamic stability. It is likely that patients initiating epinephrine at norepinephrine-equivalent doses greater than or equal to 133 μg/min were severely ill and the addition of epinephrine was not beneficial. Additionally, the data also suggest that the minimum norepinephrine dose for initiating epinephrine is 37 μg/min, which could be of value to clinicians who utilize norepinephrine doses below this threshold for initiating epinephrine.

A better understanding of when it is most beneficial to add additional vasopressors may help reduce mortality in these patients. Patients unresponsive to norepinephrine and fluid resuscitation may benefit from the additional inotropic effect of epinephrine, especially in patients with decreased cardiac output at baseline because the drug increases cardiac index and stroke volume [19]. In this study, both optimal and non-optimal dose groups had a median ScvO2 <70% with a high lactate at baseline, indicating inadequate tissue oxygen delivery [20]. However, patients receiving epinephrine at norepinephrine equivalent doses 37–133 μg/min more frequently had improved hemodynamic stability. Although this study was not designed to evaluate the mechanism for lower response rates in the non-optimal dose group, it appears that patients with refractory shock and ScvO2 threshold of <70% may not benefit from an inotropic effect [20]. Alternatively, these patients may have had impaired beta−1-adrenocrecptor activity, maximized beta-1-adrenoreceptor occupancy by norepinephrine, elevated right and/or left ventricular afterload that inotropy from epinephrine could not

Table 2
Primary and secondary outcomes.

	Optimal dose group	Non-optimal dose group	P-value
	($n = 138$)	(n = 61)	
Primary outcome			
Achieved hemodynamic stability, n (%)	40 (29)	9 (14.8)	0.03
Secondary outcomes			
Shock-free survival, n (%)	9 (6.5)	3 (4.9)	0.76
ICU mortality, n (%)	127 (92)	57 (93.4)	1.00
ICU-free days, days[a]	0.3 (0–5.4)	2.1 (0–7.7)	0.18
Hospital length of stay, days	6.7 (2.7–19)	7.9 (3.5–13.2)	0.87
Change in SOFA score at 48 h	−1 (−5 to +3)	−3.5 (−6.5 to −1.5)	0.08
Safety outcomes			
New arrhythmias, n (%)	8 (5.8)	4 (6.6)	1.00
Hyperlactatemia, n (%)	72 (52.2)	28 (45.9)	0.42
Hyperglycemia, n (%)	3 (2.2)	1 (1.6)	1.00

Continuous data presented as median (IQR).
MAP mean arterial pressure, *ICU* intensive care unit, *SOFA* sequential organ failure assessment, *IQR* interquartile range.
[a] Number of ICU-free days during hospital admission.

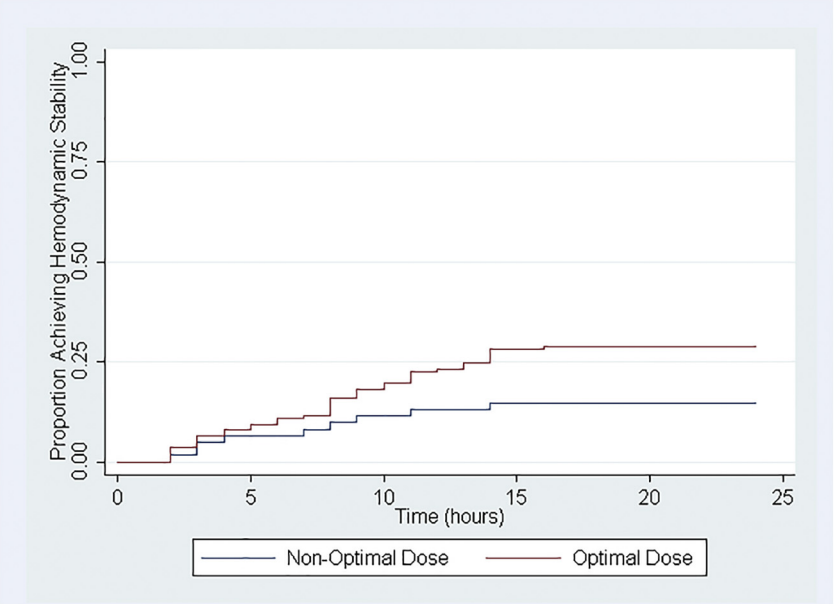

Fig. 3. Kaplan-Meier estimates based on receiving epinephrine at optimal versus non-optimal norepinephrine- equivalent dose. Optimal Dose group HR 2.09 [95% CI 1.01–4.30]; $p = .05$.

overcome, or a combination of these factors [21]. Further studies should evaluate the clinical pharmacology of epinephrine in patients with refractory septic shock in order to address these possible mechanisms.

In clinical practice in the United States, epinephrine is often used as third-line or salvage therapy when patients with septic shock are hemodynamically unstable. This is in part due to concerns for decreased gastric blood flow, arrhythmias, and increased lactate concentration [8,22]. The use of epinephrine as salvage therapy was observed in the current study, as evident by the baseline characteristics and extremely high ICU mortality rate. Even in the optimal dose group, only 29% of patients achieved hemodynamic stability after epinephrine initiation. There may be limited value of adjunctive epinephrine in the most severely ill patients with refractory shock, and the potential benefit of angiotensin II, high-dose vasopressin, alternative vasoconstrictors (e.g., methylene blue), and other rescue therapies in this patient population should be further evaluated [23].

Hyperlactatemia was common in this study, occurring in 52% of the optimal dose group and 46% of the non-optimal dose group. Elevated lactate concentrations have previously been reported with epinephrine, and it is thought that epinephrine increases aerobic glycolysis in the muscle through stimulation of β_2 receptors and the Na^+/K^+-ATPase, which increases lactate production and release from skeletal muscle [8,15,16,24]. Epinephrine-associated hyperlactatemia can lead to acidemia and confound the ability for clinicians to differentiate between worsening tissue perfusion and drug adverse reaction, limiting the clinical utility of this agent.

There are several limitations to acknowledge in this study. First, it was a retrospective, observational study and thus had limitations inherent to its study design. This study included patients between 2010 and 2016, during which the new Surviving Sepsis Campaign guidelines were released and changes in practice may have occurred, which may be unaccounted for in this evaluation. As previously mentioned, this study population was severely ill and may limit generalizability to populations that are less severely ill; however, the use of epinephrine in refractory shock is in line with current guideline recommendations [3]. Due to the retrospective nature of this study, the specific indication for initiating epinephrine could not be evaluated. Moreover, low rates of fluid resuscitation were seen in this study with only 70% of patients having fluids documented during the six hours prior to the first documented norepinephrine administration. These rates are much lower than expected for patients with septic shock and likely reflect a large number of patients transferred from another institution while receiving norepinephrine for whom fluid administration prior to the first documented norepinephrine administration would not be expected. Additionally, because only about half of the patients had ScvO2 available for analysis this variable was not included in the multivariable analysis. Therefore we were unable to thoroughly evaluate the potential impact of ScvO2 in our analysis. Additionally, the analysis of time to hemodynamic stability did not account for the competing risk of death prior to achieving hemodynamic stability. As such, the values presented in Fig. 3 and hazard ratios may overestimate the proportion achieving hemodynamic stability and rate of achieving hemodynamic stability, respectively. Finally, vasopressin was included in the calculation of the norepinephrine-equivalent doses [13]. Given the baseline difference in utilization of vasopressin, the implications of this addition to the calculation is unclear.

The CART analysis identified a specific norepinephrine-equivalent dose range at which the initiation of epinephrine achieved hemodynamic stability. However, in this study it did not translate into meaningful clinical outcomes. We hypothesize that perhaps these positive clinical outcomes were not identified due to lack of statistical power to detect these outcomes. As such, adequately powered studies should further investigate the clinical significance of these norepinephrine-equivalent dose breakpoints.

In conclusion, epinephrine initiation at a norepinephrine-equivalent dose between 37 and 133 μg/min correlated with hemodynamic stability in this study of septic shock. Thus, clinicians should consider the addition of epinephrine when doses of other vasopressors have been optimized and should not significantly delay initiation of epinephrine until the norepinephrine-equivalent dose is >133 μg/min. Norepinephrine-equivalent dose is one of many patient-specific factors that clinicians should consider when adding epinephrine in patients with septic shock.

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Conflicts of interest

All authors have declared they have no conflict of interest relevant to this work.

Declaration of conflicting interests and financial support

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.05.024.

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