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RESEARCH ARTICLE

Characteristics and Outcomes Between Patients Treated with Vasopressor Therapy Before and After Randomization in the Usual Care Arm of the ProCESS Trial

Liga Yusvirazi[1], Imoigele P. Aisiku[2], Jason E. Cohen[3], Donald M. Yealy[4], Peter C. Hou[5]

[1]Department of Emergency Medicine, Kaiser Permanente Modesto Medical Center, Modesto, CA.

[2]Department of Emergency Medicine, Stony Brook University, Stony Brook, NY.

[3]Boston MedFlight, Bedford, MA.

[4]Department of Emergency Medicine, University of Pittsburgh, Pittsburgh, PA.

[5]Division of Emergency Critical Care Medicine, Department of Emergency Medicine, Brigham and Women's Hospital, Mass General Brigham, Boston, MA.

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Corresponding Author: Peter C. Hou, MD, Division of Emergency Critical Care Medicine, Department of Emergency Medicine, Brigham and Women's Hospital, Mass General Brigham, Boston, MA, USA.

Abstract

Objective

Patients in septic shock may be treated initially with vasopressors as fluid resuscitation is ongoing in the emergency department (ED). The optimal timing of starting vasopressor therapy remains unclear. Using observations from a trial that studied therapies in early septic shock care, we sought to compare the characteristics and outcomes of patients who were treated with vasopressor therapy before and after randomization to explore any possible timing impacts.

Methods

We analyzed a usual care (wild type) subgroup from a multicentered, emergency department based resuscitative trial for those recognized and enrolled with early septic shock. We included patients who received vasopressor therapy, classifying them into two groups based on randomization time: vasopressor therapy before or after randomization. The primary outcome was 60-day in-hospital mortality. A multivariate Cox regression model was used to adjust for confounding.

Results

Overall, we identified 201 patients in the usual care group who met our evaluation criteria. Of these, 69 received vasopressor therapy before and 132 after randomization. The group receiving vasopressor before randomization had more chronic respiratory disease (37.7% vs. 20.5%), new mechanical ventilation (37.7% vs. 21.2%), received earlier antibiotics (88.4% vs. 73.5%), and had longer time to randomization after meeting inclusion criteria (78 min vs. 59 min). In the primary analysis, the group receiving vasopressor before randomization had the same risk of death at 60 days compared to those who received vasopressor after randomization [30.4% vs. 18.9% (HR 1.48; 95% CI, 0.78-2.83, p=0.23)]. The rate of new organ failure did not differ.

Conclusions

In this subanalysis of ED patients with early septic shock, the risk of 60-day in-hospital mortality was not different between patients who received vasopressor therapy before and after randomization.

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1. Introduction

1.1 Background

Fluids and vasopressors are key tools in addressing circulatory needs in those with septic shock or sepsis with hypotension. The Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) trial found no difference in 90-day mortality rates, nor safety concerns between two common fluid and vasopressor treatment strategies.[1] CLOVERS was a multicenter, prospective, phase 3 randomized non-blinded interventional trial of fluid treatment strategies (restrictive fluids strategy (vasopressors first followed by rescue fluids) vs. liberal fluid strategy (fluids first followed by rescue vasopressors) in the first 24 hours for patients with sepsis-induced hypotension on 90- day in-hospital mortality.[1]

1.2 Importance

Three large trials (ProCESS, ARISE, and ProMISe) and a follow-up patient-level meta- analysis (PRISM) showed that Early Goal Directed Therapy (EGDT), as described in 2001 by Rivers et al., was not superior to other structured or contemporary usual care.[2-4] These data, along with those from CLOVERS, leave open the ideal timing of initiating vasopressor therapy and outcomes.[5]

1.3 Goal of this investigation

We sought to examine possible timing effects of vasopressor initiation in early care of those with septic shock using data from an existing trial. We examined vasopressor therapy before and after randomization and associations with 60-day in-hospital mortality, the rate of new organ failure within the first week, and the intensive care unit (ICU) and hospital length of stay (LOS).

2. Methods

2.1 Study Design and Selection of Patients

We performed a secondary analysis of the Protocolized Care for Early Septic Shock (ProCESS) trial, a multicenter randomized clinical trial published in 2014 that compared three resuscitation strategies [EGDT, protocolized standard care (PSC), and unstructured usual care (UC)] for patients with early septic shock diagnosed in the emergency department (ED).[2] We evaluated the patients in the UC arm because the clinical providers directed all patient care without any study intervention, seeking a natural experiment condition that might better reflect daily practice and impact. We enrolled those who received vasopressor therapy and classified them into two groups based on randomization time: vasopressor therapy started before or after randomization.

2.2 Outcome Measure

The primary outcome was the 60-day all-cause in-hospital mortality. The secondary outcomes were organ failures (acute respiratory failure and acute renal failure) within the first week after randomization and ICU and hospital LOS.

2.3 Statistical Analysis

We present descriptive statistics of baseline characteristics across treatment groups as mean values with standard deviation for continuous variables and count and proportion for categorical variables. We used two-tailed chi-squared tests or t-tests to examine associations between the categorical or continuous variables.

For the primary outcome, we used a multivariate cox-proportional hazard regression model to examine the treatment effect of early vasopressor therapy, chosen because of its ability to incorporate time-varying covariates. To build the model, we selected variables that may interact with the primary outcome, such as, demographics, comorbidity, and the severity of illness; laboratory data; baseline vital signs; time to randomization; and medications prior to randomization in the UC arm. The estimate expression used a Hazard Ratio with a 95% confidence interval (CI). We generated Kaplan–Meier estimates, assessed between-group differences, and expressed the data as cumulative mortality curves. We censored patient outcomes at the end of 60 days.For the secondary outcomes, a univariate logistic regression model estimated the difference and described it as an odds ratio (OR) for organ failure that occurred within one week. The linear regression estimated the difference in the means for the length of stay between groups. All analyses utilized R statistical software, version 4.0.3, and the comparison alpha error was 0.05.

3. Results

3.1 Characteristics of Patients

In the ProCESS trial, 201 patients entered the UC arm and received vasopressor therapy. In this study cohort, the mean age was 62 years, 58% were male, and the most common co-morbid condition was hypertension (60%), followed by diabetes mellitus (37%). The

mean time from ED arrival to randomization was 179 minutes, the pre- randomization mean intravenous fluids were 2538 mL, and the mean baseline APACHE II score was 23. Respectively, 69 patients (34.3%) and 132 (65.7%) received vasopressor therapy before and after randomization. Compared to the group that received vasopressor after randomization, the group that received vasopressor before randomization had longer time to randomization from ED arrival (199 vs. 168 min) and meeting inclusion criteria (78 vs. 59 min), more chronic respiratory disease (37.7% vs. 20.5%), more intubations (37.7% vs. 21.2%), and more patients who received antibiotics (88.4% vs. 73.5%). Mean APACHE II score was similar in both groups (23.7 vs. 21.8). The patient baseline characteristics are in Table 1.

Table 1. *Baseline characteristics.*

Characteristics	All n = 201	Vasopressor before randomization n = 69 (34.3%)	Vasopressor after randomization n = 132 (65.7%)	p-value
Age (mean (SD))	62 (15.5)	65 (15)	61 (15.7)	0.10
Male gender (%)	116 (57.7)	38 (55.1)	78 (59.1)	0.69
Race (%)				0.87
White	135 (67.2)	48 (69.9)	87 (65.9)	
Black or African American	47 (23.4)	15 (21.7)	32 (24.2)	
Other	19 (9.5)	6 (8.7)	13 (9.8)	
Chronic condition				
Hypertension (%)	120 (59.7)	42 (60.9)	78 (59.1)	0.93
Diabetes mellitus (%)	74 (36.8)	24 (34.8)	50 (37.9)	0.78
Chronic respiratory disease (%)	53 (26.4)	26 (37.7)	27 (20.5)	0.01
Cancer (%)	40 (20)	15 (21.7)	25 (19.1)	0.80
Renal disease (%)	38 (18.9)	9 (13)	29 (22)	0.18
Congestive heart failure (%)	25 (12.4)	8 (11.6)	17 (12.9)	0.97
Prior myocardial infarct (%)	19 (9.5)	9 (13)	10 (7.6)	0.32
Cerebrovascular disease (%)	21 (10.4)	8 (11.6)	13 (9.8)	0.88
Peripheral vascular disease (%)	20 (10)	9 (13)	11 (8.3)	0.42
Dementia (%)	17 (8.5)	7 (10.1)	10 (7.6)	0.72
Liver Cirrhosis (%)	15 (7.5)	6 (8.7)	9 (6.8)	0.84
AIDS (%)	6 (3)	2 (2.9)	4 (3)	1.00
Immunosuppressed (%)	39 (19.4)	9 (13)	30 (22.7)	0.14
Source of sepsis (%)				0.85
Pneumonia	68 (33.8)	26 (37.7)	42 (31.8)	
Urinary tract infection	44 (21.9)	15 (21.7)	29 (22)	
Intraabdominal infection	22 (10.9)	7 (10.1)	15 (11.4)	
Other	67 (33.3)	21 (30.4)	46 (34.8)	
Positive blood culture (%)	71 (35.3)	21 (30.4)	50 (37.9)	0.37
APACHEII baseline (mean (SD))	22.5 (7.9)	23.7 (8.4)	21.8 (7.6)	0.10
Baseline condition				
Intubated (%)	54 (26.9)	26 (37.7)	28 (21.2)	0.02
MAP (mean (SD))	66.5 (19.5)	67 (21.1)	66.3 (18.6)	0.81
RR (mean (SD))	23.3 (8.1)	23.3 (7.9)	23.4 (8.3)	0.94
O2 saturation (mean (SD))	95.1 (7.7)	94 (7.7)	95.6 (7.6)	0.15
Temperature (mean (SD))	37.5 (1.6)	37 (1.8)	37.7 (1.5)	0.01
HR (mean (SD))	114 (25)	112 (26)	116 (24)	0.24
Initial lactic acid (mean (SD))	4.7 (3.3)	4.8 (3.6)	4.7 (3.1)	0.80
Time to randomization – min				
From ED arrival (mean (SD))	179.1 (106.3)	199.1 (120.7)	168.6 (96.8)	0.05
From meeting entry criteria (mean (SD))	66.1 (35.7)	78 (36.7)	59.8 (33.7)	0.001
Pre-randomization				
Steroid (%)	24 (11.9)	18 (13.6)	6 (8.7)	0.43
Fluid volume mL (mean (SD))	2538 (1495)	2623 (1580)	2494 (1453)	0.56
Antibiotics used (%)	158 (78.6)	61 (88.4)	97 (73.5)	0.02

Abbreviation: Standard deviation (SD); Acquired auto immunodeficiency syndrome (AIDS); Acute physiology and chronic health evaluation II (APACHE II); Mean arterial pressure (MAP); Respiratory rate (RR); Hear rate (HR); Emergency department (ED).

3.2 Main Results

For the primary outcome, 30.4% and 18.9% of patients who received vasopressor therapy before and after randomization died in the hospital by day 60. In the multivariate cox-proportional hazard model (Tables 3 & 4), the mortality rates did not differ with a hazard ratio of 1.39 (95% CI, 0.71 – 2.72) in the group that received vasopressor prior to randomization (Table 2, Figure 1).

Table 2. *Outcome*

Characteristics	Vasopressor before randomization n = 69	Vasopressor after randomization n=132	HR (95%CI)	p-value
Primary outcome				
In hospital mortality by day 60 (%)	21 (30.4)	25 (18.9)	1.39 (0.71 – 2.72)	0.30
Secondary outcome			OR (95% CI)	
New organ failure in the first week				
Renal (%)	4 (5.8)	2 (1.5)	4 (0.76 - 29.40)	0.12
Respiratory (%)	38 (55.1)	56 (42.4)	1.66 (0.93 - 3.01)	0.09
ICU length of stay (days) (mean (SD))	6.9 (9.1)	5.7 (5.6)		0.24*
Hospital length of stay (days) (mean (SD))	11.7 (11.8)	11.5 (10.5)		0.89*

Abbreviation: Intensive care unit (ICU); Standard deviation (SD); odds ratio (OR); Odds ratio (OR).Hazard ratio along with p-value was obtained from Multivariable cox-proportional regression. Adjusted with APACHE II, gender, dementia, hypertension, liver cirrhosis, intubated, initial lactate, criteria met to randomization time, and pre-randomization steroids. The odds ratio and the p-value for new organ failure along were obtained from simple logistic regression.

* p-value was obtained from linear regression.

Table 3. *Multivariate Cox-Proportional Hazard.*

Variable	HR (95% CI)
Pre-randomization vasopressor	1.39 (0.71 – 2.72)
Gender male	0.48 (0.25 – 0.91)
Dementia	1.26 (0.53 – 3.03)
Hypertension	1.55 (0.78 – 3.05)
Liver cirrhosis	2.05 (0.85 – 4.96)
APACHE II baseline	1.07 (1.02 – 1.12)
Intubation	1.04 (0.47 – 2.31)
Initial lactic acid	1.06 (1.00 – 1.13)
Criteria met to randomization time	1.01 (1.00 – 1.02)
Pre-randomization steroids	0.14 (0.02 – 1.08)

Abbreviation: Hazard ratio (HR); Confidence interval (CI); Acute physiology and chronic health evaluation II (APACHE II). We did not include age and temperature variables to the model because of part of APACHE II score.

Table 4. *Variables that interact with outcome.*

Characteristics	Alive n = 155	Died n = 46	p-value
Age (mean (SD))	60 (15.2)	72 (12.8)	< 0.001
Male gender (%)	96 (61.9)	20 (43.5)	0.04
Race (%)			0.98
White	104 (67.1)	31 (67.4)	
Black or African American	36 (23.2)	11 (23.9)	
Other	15 (9.7)	4 (8.7)	
Chronic condition			
Hypertension (%)	87 (56.1)	33 (71.7)	0.09
Diabetes mellitus (%)	53 (34.2)	21 (45.7)	0.22
Chronic respiratory disease (%)	42 (27.1)	11 (23.9)	0.81
Cancer (%)	29 (18.8)	11 (23.9)	0.59
Renal disease (%)	29 (18.7)	9 (19.6)	1
Congestive heart failure (%)	19 (12.3)	6 (13)	1
Prior myocardial infarct (%)	13 (8.4)	6 (13)	0.51
Cerebrovascular disease (%)	16 (10.3)	5 (10.9)	1
Peripheral vascular disease (%)	13 (8.4)	7 (15.2)	0.28
Dementia (%)	9 (5.8)	8 (17.4)	0.03
Liver Cirrhosis (%)	8 (5.2)	7 (15.2)	0.05
AIDS (%)	5 (3.2)	1 (2.2)	1
Immunosuppressed (%)	31 (20)	8 (17.4)	0.86
Source of sepsis (%)			0.67
Pneumonia	50 (32.3)	18 (39.1)	
Urinary tract infection	33 (21.3)	11 (23.9)	

Intraabdominal infection	17 (11)	5 (10.9)	
Other	55 (35.5)	12 (26.1)	
Positive blood culture (%)	54 (34.8)	17 (37)	0.93
APACHEII baseline (mean (SD))	20.9 (7.2)	27.8 (8.1)	< 0.001
Baseline condition			
Intubated (%)	31 (20)	23 (50)	< 0.001
MAP (mean (SD))	66.1 (19.5)	67.9 (19.3)	0.58
RR (mean (SD))	22.8 (8.3)	25.1 (7.4)	0.09
O2 saturation (mean (SD))	95.3 (7.8)	94.4 (7.2)	0.51
Temperature (mean (SD))	37.6 (1.6)	37 (1.8)	0.02
HR (mean (SD))	115 (25.6)	113 (24)	0.63
Initial lactic acid (mean (SD))	4.2 (2.9)	6.6 (3.7)	< 0.001
Time to randomization – min			
From ED arrival (mean (SD))	183.8 (117.5)	163.3 (51.5)	0.25
From meeting entry criteria (mean (SD))	61.7 (34.4)	80.7 (36.7)	0.001
Pre-randomization			
Steroids (%)	23 (14.8)	1 (2.2)	0.04
Fluid volume mL (mean (SD))	2600 (1546)	2330 (1301)	0.28
Antibiotics used (%)	122 (78.7)	36 (78.3)	1

Abbreviation: Standard deviation (SD); Acquired auto immunodeficiency syndrome (AIDS); Acute physiology and chronic health evaluation II (APACHE II); Mean arterial pressure; (MAP); Respiratory rate (RR); Hear rate (HR); Emergency department (ED).

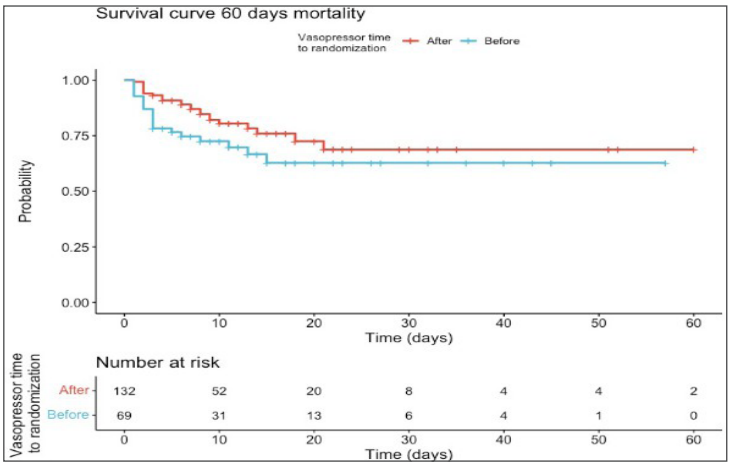

Figure 1. *Survival curve 60 days molarity*

For the secondary outcomes, there was no difference in the frequency of new acute organ failure (i.e., renal and respiratory) within one week for both groups. In addition, ICU and hospital LOS were not different between both groups (Table 2). The total intravenous fluids received over 6, 12, 24, 48, and 72 hours were not different between the two groups (Table 5).

Table 5. *Fluids Balance*

Characteristics	All n= 201	Vasopressor before randomization n = 69	Vasopressor after randomization n = 132	p-value
Fluid volume 6 hrs after randomization (mean (SD))	2447 (1987)	2092 (1710)	2632 (2099)	0.07
Fluid volume 12 hrs after randomization (mean (SD))	5838 (2659)	5542 (2811)	5992 (2574)	0.26
Fluid volume 24 hrs after randomization (mean (SD))	7046 (3351)	6666 (3749)	7245 (3120)	0.25
Fluid volume 48 hrs after randomization (mean (SD))	8451 (4325)	8004 (4810)	8684 (4049)	0.29
Fluid volume 72 hrs after randomization (mean (SD))	9355 (5200)	8776 (5810)	9657 (4847)	0.26
Fluid volume 6 to 72 hrs after randomization (mean (SD))	4693 (4304)	4428 (4638)	4832 (4131)	0.53

Fluid volume in milliliters (mL).

4. Limitations

Our observations are limited by the experimental nature of the study cohort and the natural differences in characteristics at baseline between groups. Notably, patients who received vasopressor before randomizations were older and had a higher severity of illness. The type and dose of vasopressor administered and length of time of vasopressor therapy were not standardized, a limitation though a potential pragmatic strength in trial design for generalizability. In addition, we could not differentiate which patients received simultaneous

vasopressor and fluids resuscitation versus patients who completed fluid resuscitation and then received vasopressor therapy prior to randomization, which could amplify or obfuscate any timing of vasopressor impact. Finally, resuscitation approaches may have changed in the decade since publication, notably fluid strategies, though this was closely tracked.

5. Discussion

Several studies investigated the timing of vasopressor initiation and favored "early" vasopressor administration and judicious "early" intravenous fluid resuscitation. Three cohort studies[6-8] and one single-center randomized control trial[9] supported the use of early vasopressor therapy to reduce the short-term mortality rate. However, study by Permpikul et al. showed early vasopressor administration not associated with mortality reduction.[10] Those observations of early enhanced effect are not universal. More importantly what does early vasopressor initiation really mean? As illustrated in Tables 6 and 7, the inclusion criteria of early septic shock trials and the timing of vasopressor in the studies are quite heterogeneous.

Table 6. *Inclusion Criteria of Early Septic Shock Trials*

Trial Name	Inclusion Criteria
EGDT NEJM 2001	Fulfillment of two of four criteria for the systemic inflammatory response syndrome and a systolic blood pressure no higher than 90 mm Hg (after a crystalloid-fluid challenge of 20 to 30 ml per kilogram of body weight over a 30-minute period) or a blood lactate concentration of 4 mmol per liter or more.
ProCESS NEJM 2014	• be 18 years of age • have a suspected infection • meet two or more of the criteria for systemic inflammatory response syndrome, and • have refractory hypotension (systolic blood pressure < 90 mmHg despite an intravenous [IV] fluid challenge of 1000 mL over a 30-minute period), or evidence of hypoperfusion (blood lactate concentration > 4 mmol/L). To identify refractory hypotension, we initially required a 20 mL/kg minimum crystalloid bolus over 30 minutes (identical to that of Rivers and colleagues1) but modified this to the simpler 1000 mL bolus in April 2010 to ease logistics.
ARISE NEJM 2014	All inclusion criteria are met within 6 hours of presentation to the ED and the patient is present in the ED at the time of enrolment. Patient enrolment must occur within a further 2 hours of meeting all inclusion criteria: 1. Suspected or confirmed infection AND 2. The presence of TWO or MORE of the following systemic inflammatory response syndrome (SIRS) criteria as defined by the American College of Chest Physicians (ACCP)/ Society of Critical Care Medicine (SCCM) Consensus Conference [31]: a. Core temperature < 36.0 o C or > 38.0 o C b. Heart rate > 90 beats/minute c. Respiratory rate > 20 breaths/minute or PaCO2 < 32 mmHg or the requirement for mechanical ventilation for an acute process d. White blood cell count > 12.0 or < 4.0 x109 /L or > 10% immature band forms AND 3. Evidence of either refractory hypotension OR hypoperfusion: a. Refractory hypotension is confirmed by the presence of ONE or MORE of the following: i. Systolic blood pressure (SBP) < 90 mmHg or mean arterial pressure (MAP) < 65 mmHg after a 20ml/kg intravenous fluid challenge over 60 minutes or ii. the need for vasopressor support for ≥ 30 minutes to maintain SBP ≥ 90 mmHg or MAP ≥ 65 mmHg b. Evidence of hypoperfusion is confirmed by the presence of a blood lactate concentration ≥ 4.0 mmol/L
ProMISe NEJM 2015	Following presentation at the Emergency Department, the four criteria to be met, once, in any order, over a maximum of six hours: refractory hypotension or hypoperfusion known or presumed infection two, or more, systemic inflammatory response syndrome (SIRS) criteria first dose of IV antimicrobial therapy initiated
CLOVERS NEJM 2023	A suspected or confirmed infection (broadly defined as administration or planned administration of antibiotics) Sepsis-induced hypotension defined as systolic blood pressure < 100 mmHg or MAP < 65 mmHg after a minimum of at least 1 liter of fluid (*Fluids inclusive of pre-hospital fluids; blood pressure must be below any known or reported pre-morbid baseline).

Table 7. *Timing of Vasopressor*

Study	Early group	Late group
Bai et al. 2014	Time from the onset of septic shock to initial norepinephrine administration < 2 h	Time from the onset of septic shock to initial norepinephrine administration ≥ 2 h
Permpikul et al. 2019	Median time from emergency room arrival to norepinephrine administration was 93 min	Median time from emergency room arrival to norepinephrine administration was 192 min
Elbouhy et al. 2019	Patients received initial resuscitation as simultaneous administration of crystalloid fluids (target 30 mL/kg) together with norepinephrine infusion at a starting dose of 5 µg/min administered in an external jugular peripheral cannula	Patients' resuscitation included crystalloid fluids (target 30 mL/kg) and immediate ICU transfer where norepinephrine infusion was administered only to patients with mean arterial pressure < 65 mm Hg after fluids resuscitation via a central venous catheter
Colon Hidalgo et al. 2020	The time when vasopressors were initiated ≤ 6 h	The time when vasopressors were initiated > 6 h
Ospina-Tascón et al. 2020	Vasopressor support initiated within the next hour or even before the first fluid load with resuscitative intention (FRLoad)	Patients in whom vasopressor support was started > 1 h after the FRLoad

Our finding showed that an early septic shock trial showed no signal in 60-day in- hospital mortality between the groups that received vasopressor therapy before and after randomization. The difference in clinical outcomes seen in other reports may be attributed to the decision to initiate vasopressor therapy for early septic shock, which depends on several factors: patient response, clinical resources, patient's acuity, and the clinical judgment of the providers. In our observations, some early features differed that could potentially impact the effects of the interventions, notably intubation rate and pre-randomization antibiotics. The illness severity of the group that received vasopressor before randomization may have affected the time to recruit patients into the trial, which resulted in a longer time for randomization after ED presentation and inclusion criteria were met.

The definition of early vasopressor utilization varies among previous studies, ranging from less than 1 hour to less than 6 hours. Only one study defined their early group as receiving both vasopressor therapy simultaneously with intravenous fluid resuscitation.[9] Because of the evidence gap, there is no specific sepsis guidelines recommendation on when to initiate vasopressor therapy and whether to initiate it simultaneously with intravenous fluid resuscitation or after completion of 30 cc/kg of intravenous fluid resuscitation.[5]

We observed no difference in the hospital and ICU LOS between the two groups. This aligns with observations in previous studies.[6,7,8] Additionally, the incidence of acute organ failure, encompassing renal and respiratory dysfunction within the initial week of treatment, did not show any difference between the groups, aligning with earlier study findings.[8,9,10] It is noteworthy, however, that one study reported an increase in urine output within six hours following early vasopressor administration. Nonetheless, this effect did not translate into significant difference between the groups in terms of renal failure incidence in our study.[10]

Our findings add to the growing body of evidence supporting the notion that early vasopressor initiation in the ED is not associated with an increased 60-day in-hospital mortality rate. This observation underscores the need for further exploration through prospective clinical trials to establish a more comprehensive understanding of randomizing patients already on vasopressor therapy or not on vasopressor therapy into early septic shock trials.

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