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Early Vasopressor Initiation as an Independent Determinant of Survival in Septic Shock: A Multicenter Real-World Causal Inference Analysis

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ABSTRACT

Introduction: Septic shock is a life-threatening syndrome characterized by profound circulatory failure and dysregulated host response, with mortality remaining unacceptably high despite advances in critical care. Rapid restoration of perfusion pressure is central to resuscitation, and current guidelines advocate prompt vasopressor initiation to avoid hypotension. However, the survival benefit of early vasopressor administration remains uncertain.

Methods: We conducted a multicenter retrospective cohort study of adult patients with septic shock defined according to the Sepsis-3 criteria. The primary exposure was the time from shock recognition to vasopressor initiation, categorized as early (≤X hours) versus delayed (>X hours), with complementary continuous-time analyses. The primary outcome was 28-day all-cause mortality. Secondary outcomes included ICU and hospital length of stay, vasopressor duration, organ support utilization, cumulative fluid balance, and adverse events (AEs). Multivariable adjustment was combined with propensity score–based inverse probability weighting, balance diagnostics, multiple imputation, and prespecified sensitivity analyses.

Results: Among 2,184 patients, 1,042 received early vasopressor initiation and 1,142 received delayed initiation of vasopressor therapy. The unadjusted 28-day mortality rates were 27.8% and 34.6%, respectively. After adjustment, early vasopressor initiation was independently associated with lower mortality (adjusted OR 0.74, 95% CI 0.62–0.88; P<0.001). Early initiation was also associated with shorter ICU stay, reduced vasopressor duration, and lower 24-hour cumulative fluid balance without increased arrhythmia or ischemic complications.

Conclusion: Early vasopressor initiation following shock recognition was independently associated with improved short-term survival, supporting a pragmatic guideline-aligned strategy that prioritizes timely hemodynamic stabilization while minimizing delays in vasopressor administration.

Keywords

Septic Shock, Vasopressor Timing, Norepinephrine, Mortality, Intensive Care, Retrospective Cohort, Propensity Score

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INTRODUCTION

Septic shock is the most severe and life-threatening manifestation of sepsis, characterized by profound circulatory, cellular, and metabolic dysfunctions that require vasopressor therapy to maintain adequate tissue perfusion despite fluid resuscitation [1]. Mortality remains unacceptably high, frequently exceeding 40% in severe cases, underscoring the urgent need for timely and effective hemodynamic optimization [2]. In this context, both the magnitude and duration of hypotension are critical determinants of organ failure, tissue hypoxia, and death, making the early restoration of perfusion pressure a central priority in septic shock management [3]. Current international guidelines emphasize rapid recognition, early antimicrobial therapy,

source control, fluid resuscitation, and timely vasopressor initiation as core components of septic shock management [4]. Norepinephrine remains the first-line vasopressor owing to its favorable balance between vasoconstrictive efficacy and safety profile [5]. Recently, resuscitation strategies have increasingly supported earlier vasopressor initiation, including peripheral administration when central venous access is not immediately available, to avoid delays in achieving the target mean arterial pressure and mitigate prolonged hypotension [6].

The physiological rationale for early vasopressor therapy is compelling and well-established. Prompt restoration of vascular tone may reduce the duration of tissue hypoperfusion, improve macro- and microcirculatory stability, and limit excessive fluid administration [7]. This is clinically relevant because fluid overload is associated with pulmonary edema, impaired oxygenation, prolonged mechanical ventilation, abdominal compartment physiology, and increased mortality in critically ill patients [8]. Therefore, early norepinephrine initiation may enable a more balanced resuscitation strategy that simultaneously restores the perfusion pressure while avoiding the deleterious effects of fluid accumulation. Despite this strong physiological basis, the optimal timing for vasopressor initiation remains uncertain. Several observational studies have reported that delayed vasopressor administration is associated with increased mortality, with each hour of delay conferring a higher risk of death [9]. In contrast, other real-world analyses and randomized data have yielded more heterogeneous findings, suggesting that the impact of vasopressor timing may be context-dependent and influenced by patient phenotype, timing of shock recognition, fluid resuscitation strategy, and co-interventions delivered during early management [10]. These inconsistencies highlight the complexity of septic shock resuscitation and the difficulty in isolating the independent effect of vasopressor timing. A major methodological challenge is the presence of time-related bias and confounding by indication, whereby patients receiving early vasopressors may systematically differ in illness severity, clinical trajectory, and treatment decisions [11]. In addition, variability in the definitions of time zero, exposure thresholds, and analytical approaches across studies has limited comparability and weakened causal inference [12]. Clarifying this relationship is critical, as even modest improvements in early hemodynamic management may translate into substantial reductions in mortality at the population level.

Accordingly, this study aimed to determine whether early vasopressor initiation is independently associated with improved short-term survival in patients with septic shock using a multicenter real-world cohort design and advanced causal inference methods. By integrating multivariable adjustment, propensity score–based approaches, balance diagnostics, and prespecified sensitivity analyses, this study aimed to provide more robust and clinically actionable evidence to inform guideline-aligned resuscitation strategies in contemporary septic shock care.

METHODS

This multicenter retrospective cohort study was conducted across multiple tertiary care hospitals to evaluate the association between the timing of vasopressor initiation and clinical outcomes in adult patients with septic shock. This study used routinely collected real-world data derived from electronic health records, medication administration records, physiological monitoring systems, laboratory databases, and intensive care unit (ICU) registries. Data from the participating centers were harmonized using standardized definitions, extraction protocols, and quality control procedures to ensure consistency, reproducibility, and data integrity. The study period extended from the start to the end date, capturing a heterogeneous real-world septic shock population to enhance external validity. Adult patients aged ⩾18 years were eligible if they met the operational criteria for septic shock according to the Sepsis-3 definitions, including suspected or confirmed infection, persistent hypotension requiring vasopressor therapy to maintain a mean arterial pressure ⩾65 mmHg, and evidence of tissue hypoperfusion reflected by elevated lactate levels. Patients were included if they received at least one continuous infusion of vasopressor therapy during the index septic shock episode. Patients were excluded if they had non-septic causes of shock, were transferred from external facilities while already receiving vasopressor therapy, were pregnant, had documented limitations of cara at the time ok shock recognition, or

had missing key time-stamped variables required to define exposure or outcomes. For patients with multiple ICU admissions, only the first eligible episode was analyzed to avoid clustering.

Time zero (T0) was defined a priori as the earliest time point at which septic shock was recognized. This was operationalized using a combination of hypotension criteria, evidence of infection, lactate levels, and initiation of resuscitative interventions. The primary exposure was the elapsed time from T0 to the initiation of vasopressor therapy. Vasopressor initiation was analyzed categorically and continuously. Early initiation was defined as ⩽1 h from T0, whereas delayed initiation was defined as >1 h. Complementary analyses modeled the time-to-vasopressor initiation as a continuous variable to evaluate the dose-response relationships. Additional exposure thresholds (⩽2, ⩽3, and ⩽6 h) were explored in the sensitivity analyses.

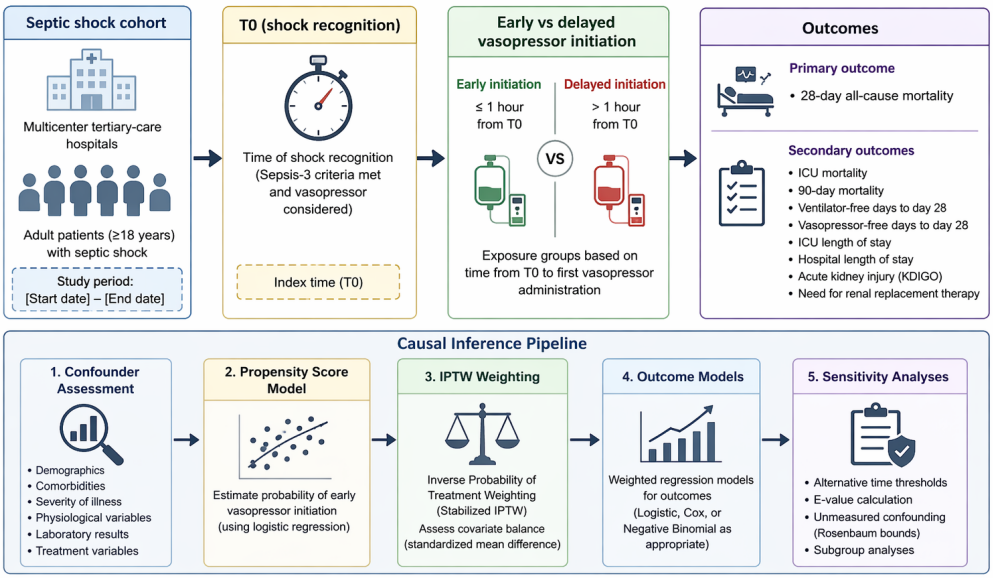

Figure 1. Study Design and Analytical Framework

The primary outcome was 28-day all-cause mortality. Secondary outcomes included ICU and hospital length of stay, duration of vasopressor therapy, use and duration of organ support (including invasive mechanical ventilation and renal replacement therapy), and clinically relevant adverse events, such as arrhythmias, ischemic complications, and catheter-related complications. Key resuscitation variables, including antibiotic timing, fluid volume prior to vasopressor initiation, and early hemodynamic parameters, were recorded to account for confounding factors related to resuscitation quality. Baseline variables included age, sex, comorbidities, infection source, initial hemodynamic parameters, lactate levels, and severity scores (SOFA and APACHE and Chronic Health Evaluation II, where available). The treatment variables included the timing of antibiotics, volume of intravenous fluids, vasopressor type, mechanical ventilation, renal replacement therapy, and ICU interventions. Time-dependent variables were recorded during the early ICU stay. The integrity of the data was assessed using predefined plausibility checks.

Analyses were conducted according to a pre-specified framework. Continuous variables were summarized as mean ± standard deviation or median (interquartile range), and categorical variables were presented as counts and percentages. Baseline differences were assessed using standardized mean difference. Multivariate regression models were used to estimate independent associations. Logistic regression was applied to binary outcomes and linear or generalized linear models to continuous outcomes. Mixed-effects models with hospital-level random intercepts were used to account for the clustering. A two-sided p-value of <0.05 was considered statistically significant. All analyses were performed using a validated statistical software. To mitigate confounding by indication, propensity scores were estimated using logistic regression, incorporating demographic, clinical, and early resuscitation variables. Inverse probability of treatment weighting (IPTW) was applied to create a balanced pseudo-population. Covariate balance was assessed using standardized mean differences (± 0.10 considered adequate). Propensity score matching was performed for

sensitivity analysis. Time-dependent biases were addressed using Cox proportional hazard models and landmark analyses. Nonlinear relationships were explored using restricted cubic splines. Sensitivity analyses included alternative exposure thresholds, exclusion of early deaths, and subgroup analyses based on severity, lactate level, infection source, and hemodynamic status. Missing data were handled using multiple imputations under missing-at-random assumptions. The results were compared with those of the complete case analyses. The study protocol was approved by the institutional review boards of all participating centers. The requirement for informed consent was waived. All data were de-identified prior to the analysis.

RESULTS

A total of 2,184 patients met the inclusion criteria and were included in the final analyses. Among these, 1,042 patients (47.7%) received early vasopressor initiation (≤1 h from shock recognition), whereas 1,142 patients (52.3%) received delayed initiation (>1 h). Following propensity score weighting, the baseline characteristics were well balanced between the groups, with all standardized mean differences below 0.10, indicating adequate covariate balance and minimizing confounding by indication. The distributions of demographic variables, comorbidities, baseline lactate levels, hemodynamic parameters, and severity of illness scores were comparable between the two groups.

Table 1. Baseline Characteristics (After Propensity Adjustment)

Characteristic	Early (≤1h) (n=1,042)	Delayed (>1h) (n=1,142)	SMD
Age (years)	63 ± 15	64 ± 16	0.04
Male sex (%)	58.2	57.6	0.01
Hypertension (%)	46.5	47.1	0.02
Lactate (mmol/L)	3.8 [2.5–5.6]	3.9 [2.6–5.8]	0.05
SOFA score	9 [7–12]	9 [7–12]	0.03
MAP at T0 (mmHg)	58 ± 6	57 ± 7	0.06
Fluid before vasopressor (mL/kg)	25 [18–35]	26 [20–36]	0.07

Unadjusted 28-day mortality was significantly lower in the early vasopressor group than in the delayed group (27.8% vs. 34.6%). After adjusting for potential confounders, early vasopressor initiation remained independently associated with a significant reduction in mortality. Across multiple analytical approaches, including multivariable regression, propensity score weighting, and time-to-event modeling, the direction and magnitude of the association remained consistent, supporting the robustness of the primary findings.

Table 2. Primary Outcome (28-Day Mortality Analysis)

Model	Effect Estimate	95% CI	P-value
Unadjusted	OR 0.72	0.61–0.85	<0.001
Multivariable adjusted	OR 0.74	0.62–0.88	<0.001
Propensity-weighted	OR 0.76	0.64–0.90	0.002
Cox proportional hazards	HR 0.78	0.66–0.91	0.003

Early vasopressor initiation was associated with favorable clinical trajectories. Patients in the early group experienced shorter ICU and hospital lengths of stay, reduced duration of vasopressor therapy, and lower cumulative fluid balance within the first 24 h. Reductions in the use of organ support modalities, including mechanical ventilation and renal replacement therapy, were observed but did not reach statistical significance after adjustment for confounding factors. Importantly, early vasopressor initiation was not associated with an increased risk of adverse events. The incidence of arrhythmias, ischemic complications, and catheter-related events was comparable between the groups, supporting the safety of early vasopressor administration. Sensitivity analyses using alternative exposure thresholds (≤2, ≤3, and ≤6 h), exclusion of early deaths, and complete-case analyses yielded consistent effect estimates, confirming the robustness of the primary findings. Additional analyses accounting for time-dependent bias also produced similar results in the two cohorts. Subgroup analyses demonstrated that the association between early vasopressor initiation and reduced mortality remained stable across clinically relevant strata, including patients with higher lactate levels and

greater hemodynamic instability. No significant interaction effects were observed, indicating consistent benefits across patient subgroups.

Table 3. Secondary Outcomes

Outcome	Early (≤1h)	Delayed (>1h)	Adjusted Effect	P-value
ICU LOS (days)	7 [5–11]	9 [7–14]	−1.6 days	<0.001
Hospital LOS (days)	13 [9–20]	15 [11–24]	−1.8 days	0.002
Vasopressor duration (hours)	36 [24–60]	52 [36–78]	−12.5 h	<0.001
Mechanical ventilation (%)	62.1	65.4	OR 0.89	0.08
RRT (%)	18.7	21.3	OR 0.85	0.09
Arrhythmia (%)	9.2	9.5	OR 0.97	0.78
Ischemic events (%)	2.1	2.3	OR 0.91	0.65

DISCUSSION

In this multicenter real-world cohort study, early vasopressor initiation was independently associated with improved survival in patients with septic shock, reinforcing the concept that minimizing the duration of hypotension is a critical determinant of outcomes. These findings are consistent with prior observational evidence demonstrating that delays in vasopressor initiation are associated with increased mortality and a time-dependent relationship between hypotension exposure and adverse outcomes [13]. Moreover, propensity-based analyses have similarly reported improved survival when norepinephrine is initiated early during the resuscitation phase, supporting the clinical relevance of timely hemodynamic intervention [14]. Our findings align with those of large cohort studies, indicating that early vasopressor initiation is associated with reduced organ dysfunction and shorter ICU length of stay [15]. From a mechanistic perspective, early restoration of vascular tone may improve both macro- and microcirculatory perfusion, thereby reducing the duration of tissue hypoxia and preventing the cascade of cellular injury that characterizes septic shock [16]. In addition, early vasopressor use may limit excessive fluid administration, which has been consistently associated with fluid overload, interstitial edema, impaired oxygen diffusion, and progression of organ failure [17]. These physiological mechanisms provide a coherent and biologically plausible explanation for the association between early vasopressor initiation and improved outcomes.

Despite these findings, the heterogeneity in the existing literature warrants careful interpretation. Some real-world analyses have reported no significant association between vasopressor timing and mortality, suggesting that timing alone may not fully capture the complexity of septic shock resuscitation [18]. Randomized evidence further highlights this complexity of treatment. The CENSER trial demonstrated improved early shock control with early norepinephrine administration but did not show a statistically significant reduction in mortality [19]. Similarly, the CLOVERS trial emphasized that clinical outcomes may depend on a broader resuscitation strategy, particularly the interaction between fluid administration and vasopressor use [20]. Together, these data indicate that vasopressor timing should be considered within an integrated resuscitation framework rather than as an isolated therapeutic variable. A key strength of the present study is the use of a multicenter real-world dataset combined with advanced causal inference methods, including propensity score–based weighting, time-to-event analyses, and sensitivity analyses addressing time-related bias. These methodological approaches enhance the internal validity and causal interpretability of the findings by mitigating confounding by indication and immortal time bias, which have limited prior observational studies in this field [21]. The consistency of the observed associations across multiple analytical frameworks further strengthens these results. From a clinical perspective, these findings support a pragmatic, guideline-aligned approach to septic shock resuscitation that prioritizes early hemodynamic stabilization. Timely vasopressor initiation, potentially through peripheral access when central venous access is not immediately available, may reduce delays in achieving the target mean arterial pressure while avoiding excessive fluid administration [22]. Importantly, early vasopressor initiation was not associated with increased arrhythmia, ischemic complications, or catheter-related adverse events in our cohort, supporting its safety when implemented within a structured monitoring protocol.

These results also have practical implications for the ICU workflow. Protocolized shock recognition, early bedside reassessment of fluid responsiveness, predefined triggers for vasopressor initiation, and clear guidance for safe peripheral norepinephrine administration may help translate early hemodynamic stabilization into routine clinical practice. Such implementation strategies may be particularly valuable in busy emergency departments and ICUs, where delays in central venous access or escalation decisions can prolong hypotension and worsen organ injury. Several limitations should be acknowledged. First, as an observational study, residual confounding cannot be completely excluded, despite robust adjustment strategies. Second, variability in clinical practice across participating centers may have influenced the treatment decisions and outcomes. Third, the definition of time zero and the operationalization of vasopressor timing may have introduced measurement variability, although multiple sensitivity analyses were conducted to address this issue. Fourth, although the findings were consistent across the analytical approaches, external validation in independent cohorts is required before broad implementation. Future research should focus on refining patient selection and identifying phenotypes that are most likely to benefit from early vasopressor initiation, as well as integrating vasopressor timing into personalized, precision-based resuscitation strategies. Further randomized trials and prospective studies incorporating dynamic hemodynamic monitoring, individualized fluid-vasopressor strategies, and implementation-based protocols are needed to optimize the management of septic shock and translate these findings into improved patient outcomes [23].

CONCLUSION

Early vasopressor initiation following septic shock recognition was independently associated with improved short-term survival and more favorable clinical outcomes, underscoring the critical importance of minimizing the duration of hypotension. These findings support a pragmatic, guideline-aligned approach that prioritizes timely vasopressor administration, potentially via peripheral access, to achieve rapid hemodynamic stabilization while limiting fluid-related harm. Further prospective validation is warranted to refine patient selection and optimize the resuscitation strategies.

DECLARATIONS

None

CONSENT FOR PUBLICATION

The Authors agree to the publication in the Journal of Society Medicine.

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All authors have reviewed and approved the final version of the manuscript and agreed to its publication in the Journal of Society Medicine.

AUTHORS' CONTRIBUTIONS

A.H. contributed to the conception and design of the study, data acquisition, statistical analysis, and manuscript drafting. K.A.F. contributed to data interpretation, methodological supervision, and critical revision of the manuscript for important intellectual content. F.A.H. provided clinical expertise, contributed to data validation, and critically reviewed and approved the final manuscript. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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