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ORIGINAL RESEARCH

Impact of Early versus Delayed Vasopressin Initiation on 28-Day Mortality in Older Adults with Septic Shock

Lina Liu[1], Haina Shi[2], Lei Zhang[3], Jiagui Ma[1]

[1]Department of Critical Care Medicine & Emergency Medicine Center, Beijing Rehabilitation Hospital Affiliated to Capital Medical University, Beijing, People's Republic of China; [2]Nursing Department, Beijing Rehabilitation Hospital Affiliated to Capital Medical University, Beijing, People's Republic of China; [3]Department of Emergency Medicine, Aerospace Center Hospital, Beijing, People's Republic of China

Correspondence: Lina Liu, Department of Critical Care Medicine & Emergency Medicine Center, Beijing Rehabilitation Hospital Affiliated to Capital Medical University, No. 15 Xixiazhuang South Road, Badachu, Shijingshan District, Beijing, 100043, People's Republic of China, Tel +86-010-56981371, Email majiaguibj@163.com

Background: The optimal timing for initiating adjunctive vasopressin in septic shock remains controversial, with limited evidence specific to older adults who may have altered physiological responses. This study aimed to investigate the association between the timing of vasopressin initiation and 28-day mortality in older adults with septic shock.

Methods: In this retrospective observational cohort study, we enrolled 197 older adults (≥65 years) with septic shock who received vasopressin within 72 hours of norepinephrine initiation. Patients were categorized into an early group (vasopressin within 6 hours of norepinephrine; n=119) and a delayed group (vasopressin between 6–72 hours; n=78). The primary outcome was 28-day all-cause mortality, analyzed using multivariable Cox regression adjusting for potential confounders.

Results: The 28-day mortality was significantly lower in the early vasopressin group compared to the delayed group (36.1% vs. 57.7%, $p<0.01$). In the multivariate Cox analysis, early initiation was independently associated with a reduced risk of 28-day mortality (HR = 0.48, 95% CI: 0.31–0.74, $p < 0.01$). Secondary outcomes also favored the early group, including a higher rate of hemodynamic response (62.2% vs. 44.9%, $p=0.02$), more mechanical ventilation-free days (11.9 vs. 8.4 days, $p=0.03$) and more continuous renal replacement therapy (CRRT)-free days (13.2 vs. 9.5 days, $p=0.03$).

Conclusion: In older adults with septic shock, early initiation of vasopressin within six hours of norepinephrine commencement was independently associated with significantly lower 28-day mortality and improved hemodynamic and organ function outcomes.

Keywords: older adults, vasopressin, septic shock, mortality

Introduction

Sepsis remains a major cause of morbidity and mortality worldwide, affecting nearly 49 million people and leading to more than 11 million deaths annually.[1] Septic shock, the most severe form of sepsis, is characterized by profound circulatory and metabolic abnormalities resulting in life-threatening organ dysfunction. Older adults are particularly at risk due to impaired cardiovascular reserve and reduced physiological adaptability.[2,3] In China, sepsis deaths decreased from 1.86 million in 1990 to 1.24 million in 2012, then rose slightly to 1.40 million in 2021, with the majority (~870,000) occurring in adults aged 70 and above, and mortality increasing sharply after age 80.[4] Despite advances in critical care, optimizing hemodynamic support in this high-risk population continues to be a significant challenge.

Vasopressor therapy is essential in managing septic shock when adequate tissue perfusion cannot be achieved with fluid resuscitation alone. The pathophysiology of septic shock is characterized by profound vasodilation, endothelial dysfunction, and impaired vascular responsiveness, leading to distributive shock and persistent hypotension.[5] In addition to excessive nitric oxide production and inflammatory mediator release, patients with septic shock often develop a relative deficiency of endogenous vasopressin during the later stages of shock.[6] This phenomenon, sometimes referred to as "vasopressin

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depletion," contributes to refractory vasoplegia and reduced responsiveness to catecholamines.[7] Consequently, adjunctive vasopressin therapy has been proposed as a strategy to restore vascular tone through non-catecholaminergic pathways and reduce exposure to high-dose catecholamines.[8,9] Norepinephrine is the recommended first-line vasopressor according to the Surviving Sepsis Campaign guidelines, with vasopressin serving as an adjunctive agent when target mean arterial pressure (MAP) is not attained. However, the optimal timing of vasopressin initiation remains controversial.[10] Early vasopressin administration may reduce catecholamine exposure, prevent β-adrenergic toxicity, improve microcirculatory flow, and potentially mitigate vasoplegia during the early phase of septic shock.[11] In contrast, delayed initiation may allow prolonged hypotension and persistent end-organ hypoperfusion, potentially worsening clinical outcomes.[6,12]

Large randomized controlled trials such as VASST and VANISH did not show a significant mortality benefit with vasopressin compared with norepinephrine alone.[13,14] However, post hoc analyses and subsequent meta-analyses suggested potential advantages when vasopressin was initiated in patients with less severe shock, lower lactate levels, and without established acute kidney injury.[14,15] Most recently, a multicenter retrospective study by White et al demonstrated that early adjunctive vasopressin initiation was independently associated with lower hospital mortality.[16] These findings highlight the potential clinical importance of timely vasopressin initiation.

Nevertheless, prior studies have focused primarily on general adult populations and have not specifically examined older adults, who may respond differently to vasopressors due to age-related alterations in vascular responsiveness and baroreceptor sensitivity.[17] The balance between benefit and risk in this subgroup remains uncertain. Therefore, this study aimed to investigate the association between the timing of vasopressin initiation and 28-day mortality in older adults with septic shock. By focusing on this distinct population, we sought to clarify whether early vasopressin initiation confers survival benefit and to provide evidence for individualized vasopressor strategies in geriatric critical care.

Materials and Methods

Study Design and Population

This was a retrospective, observational cohort study conducted in the intensive care unit (ICU) of a tertiary hospital between January 2021 and December 2023. Older adults (≥65 years) who met the diagnostic criteria for septic shock according to the Sepsis-3 definition[18] were screened for inclusion. Septic shock was defined as the requirement for vasopressor therapy to maintain a mean arterial pressure (MAP) ≥65 mmHg despite adequate fluid resuscitation, accompanied by a serum lactate concentration >2 mmol/L. Adequate fluid resuscitation was assessed in accordance with the Surviving Sepsis Campaign guidelines and routine clinical practice. In general, patients received an initial fluid resuscitation with intravenous crystalloids (typically approximating 30 mL/kg) prior to or concurrent with vasopressor initiation. However, due to the retrospective nature of the study, the assessment of adequate fluid resuscitation was not protocolized and was based on the treating clinicians' judgment in real-world practice, taking into account individual hemodynamic status and risk of fluid overload.

Patients were included if they received continuous norepinephrine infusion as the initial vasopressor, followed by vasopressin as an adjunct within 72 hours after the onset of vasopressor therapy. Exclusion criteria included: (1) postoperative or trauma-related ICU admissions; (2) vasopressin started more than 72 hours after vasopressor initiation; (3) preexisting end-stage renal disease or chronic liver failure; (4) transfer from another ICU; and (5) missing key clinical or laboratory data. Key variables were defined as those essential for outcome assessment and multivariable adjustment, including age, sex, APACHE III score, SOFA score, lactate level, norepinephrine dose at vasopressin initiation, and 28-day mortality. A complete-case analysis approach was adopted.

Data Collection

Clinical data were extracted from electronic medical record systems, including baseline demographics (age, sex, body mass index [BMI]), comorbidities, severity scores, laboratory parameters, organ support, and anti-infective therapies. The Acute Physiology and Chronic Health Evaluation (APACHE III) and Sequential Organ Failure Assessment (SOFA) scores were calculated on the day of ICU admission.

The duration and cumulative dose of vasopressor therapy were also documented. In accordance with previous studies,[13,16] patients were categorized into two groups based on the timing of vasopressin initiation relative to the start of vasopressor therapy: 1) early initiation group as vasopressin started within 6 hours of norepinephrine initiation; and delayed initiation group as vasopressin started between 6 and 72 hours after norepinephrine initiation. The choice of 6 hours as the cutoff was based on prior evidence suggesting that early adjunctive vasopressin may reduce catecholamine exposure and improve outcomes.

Vasopressor management followed standard critical care practices rather than a strictly protocolized approach. Norepinephrine was used as the first-line vasopressor and titrated to maintain a target mean arterial pressure (MAP) of ≥65 mmHg, in accordance with current guidelines. Vasopressin was administered as an adjunctive vasopressor, typically initiated at a fixed dose of 0.03 U/min without further titration. The decision to initiate vasopressin was made by the treating clinicians based on hemodynamic status, including persistent hypotension despite norepinephrine therapy, increasing norepinephrine requirements, and/or evidence of inadequate tissue perfusion such as elevated lactate levels. The duration and discontinuation of vasopressin were determined by clinical response, including stabilization of MAP and reduction in vasopressor requirements.

Outcomes

The primary outcome was 28-day all-cause mortality. Secondary outcomes included hemodynamic response to vasopressin, the duration of norepinephrine and vasopressin, the duration of mechanical ventilation-free days at day 28, and the duration of ICU and hospital stays. Hemodynamic response to vasopressin was defined as the achievement of both at least a 20% decrease from baseline in norepinephrine dose and MAP ≥ 65 mm Hg at 6 h after initiation of vasopressin. When the patients were alive, the mechanical ventilation-free days were calculated as the number of days out of 28 days. If patients died within 28 days, the free days were defined zero.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation (SD) or median with interquartile range (IQR) depending on data distribution, and categorical variables as counts and percentages. Between-group differences were assessed using the Student's *t*-test or Mann–Whitney *U*-test for continuous variables, and the chi-square or Fisher's exact test for categorical variables.

Univariate Cox regression was first performed for the following candidate variables: age, sex, body mass index, comorbidities (eg., diabetes, hypertension, chronic heart failure), SOFA score, APACHE III score, initial hemodynamic parameters (mean arterial pressure, heart rate), laboratory values at shock onset (maximum lactate, creatinine, bilirubin, platelet count), fluid balance within the first 24 hours, and vasopressor requirements (norepinephrine dose at vasopressin initiation). Variables with $p < 0.1$ in univariate analysis were then included in the multivariable Cox model. This approach ensured a parsimonious model while maintaining adjustment for key confounders.

Time-zero for all survival analyses, including Kaplan–Meier curves and Cox proportional hazards modeling, was defined as the initiation of norepinephrine therapy, which marked the onset of vasopressor-dependent septic shock. Patients were classified into early and delayed vasopressin groups based on the time interval from norepinephrine initiation. We acknowledge that the classification of exposure based on post-baseline events may introduce potential time-dependent bias. To mitigate this, all patients entered the risk set at a uniform time point (norepinephrine initiation), and key indicators of disease severity at the time of vasopressin initiation were adjusted for in the multivariable model.

To assess the robustness of our findings to missing data, a sensitivity analysis using multiple imputations was performed. Missing values for key covariates were imputed using multiple imputations by chained equations (MICE) method with 20 iterations. Cox proportional hazards regression was repeated on the imputed datasets to examine the association between early versus delayed vasopressin initiation and 28-day mortality.

All statistical analyses were performed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed p value <0.05 was considered statistically significant.

Results

Baseline Characteristics

During the study period, 270 patients with septic shock were screened for eligibility. Seventy-three patients were excluded for the following reasons: postoperative or trauma-related ICU admission (n = 20), vasopressin initiation more than 72 hours after norepinephrine (n = 18), preexisting end-stage renal disease or chronic liver failure (n = 14), transfer from another ICU (n = 12), and missing key clinical or laboratory data (n = 9). Ultimately, 197 patients were included in the final analysis (Figure 1), of whom 119 (60.4%) received early vasopressin initiation (within 6 hours of norepinephrine start) and 78 (39.6%) received delayed initiation (6–72 hours). The overall proportion of missing data was low (<5%), and no significant differences in missingness were observed between the early and delayed groups.

Baseline characteristics were generally comparable between the two groups (Table 1). Age, gender and the prevalence of major comorbidities, including diabetes mellitus, chronic heart failure, chronic obstructive pulmonary disease (COPD), and liver disease, did not differ significantly between groups (all $p > 0.05$). The severity of illness at ICU admission, assessed by APACHE III and SOFA scores, was similar in both groups (both $p > 0.05$). However, at the time of vasopressin initiation, patients in the early group had higher norepinephrine requirements ($p = 0.03$) and higher peak lactate levels ($p < 0.01$), suggesting a more severe circulatory dysfunction.

Primary Outcome

As shown in Table 2, the 28-day all-cause mortality was significantly lower in the early vasopressin group compared with the delayed group (36.1% vs. 57.7%, $p < 0.01$). Kaplan–Meier survival analysis demonstrated a significantly higher cumulative survival probability in the early vasopressin group than in the delayed group (Log rank test, $p < 0.05$; Figure 2).

In univariate Cox regression analysis (Table 3), early vasopressin initiation, APACHE III score, SOFA score, and dobutamine use showed associations with 28-day mortality ($p < 0.10$) and were therefore included in the multivariable Cox model. In the multivariable analysis, early vasopressin initiation remained independently associated with lower 28-day mortality (HR = 0.48, 95% CI: 0.31–0.74, $p < 0.01$), while higher APACHE III (HR = 1.05, 95% CI: 1.03–1.06, $p < 0.01$) and SOFA scores (HR = 1.26, 95% CI: 1.19–1.35, $p < 0.01$) were independently associated with increased mortality. No other variables retained statistical significance in the adjusted model.

The results of the multiple imputation analysis were consistent with those of the primary complete-case analysis. Missing data were minimal, affecting 5 patients in the early vasopressin group and 4 in the delayed group. After multiple imputation, early vasopressin initiation remained significantly associated with lower 28-day mortality (pooled HR = 0.49, 95% CI: 0.32–0.75, $p < 0.01$), supporting the robustness of the primary findings.

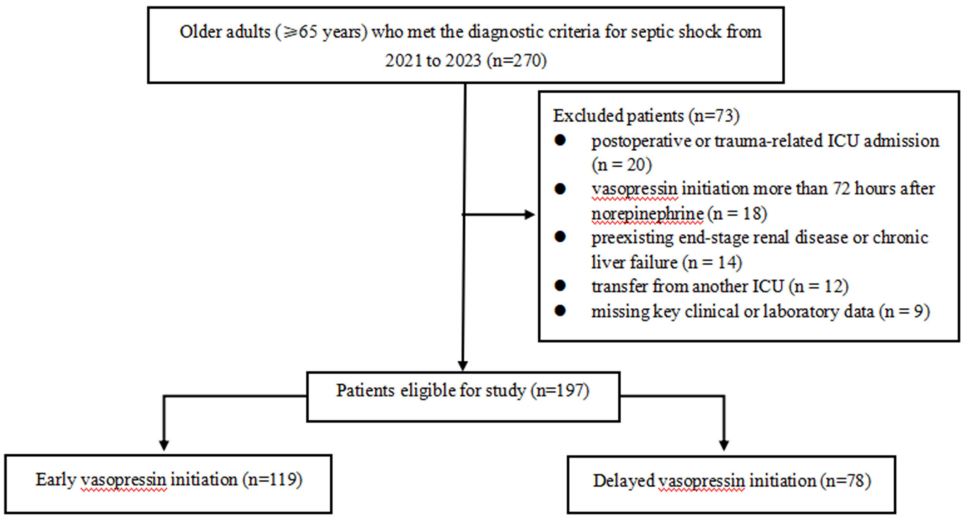

Figure 1 The flowchart of study population selection.

Table 1 Baseline Characteristics of the Cohort According to the Vasopressin Start Time

	Early Start	Late Start	*p* value
N	119	78	
Demographic			
Age, years	69.7±2.7	70.2±2.8	0.49
Female, n (%)	42 (35.3%)	37 (47.4%)	0.09
Body mass index, kg/m^2	24.1±1.7	24.0±1.7	0.64
Comorbidities, n (%)			
Diabetes mellitus	43 (36.1%)	21 (26.9%)	0.18
Chronic heart failure	32 (26.9%)	19 (24.4%)	0.69
COPD	28 (23.5%)	16 (20.5%)	0.62
Chronic renal disease	28 (23.5%)	11 (14.1%)	0.10
Liver disease	32 (26.9%)	16 (20.5%)	0.31
Stroke	11 (9.2%)	6 (7.7%)	0.71
Malignancy	20 (16.8%)	13 (16.7%)	0.98
Scoring system			
APACHE III score	96.4±19.7	94.1±23.3	0.46
SOFA score	8.2±4.0	8.8±4.2	0.34
Characteristics at vasopressin initiation			
Mechanical ventilation, n (%)	41 (34.5%)	31 (39.7%)	0.45
CRRT, n (%)	5 (4.2%)	4 (5.1%)	0.76
NE dose, ug/kg/min	0.27±0.09	0.24±0.07	0.03
Maximum lactate, mmol/L	5.6±0.9	4.5±0.9	<0.01
Vasopressin start time, hour	1.6±0.9	14.5±4.6	<0.01
Medications, n (%)			
Antibiotics	115 (96.6%)	73 (93.6%)	0.32
Hydrocortisone	38 (31.9%)	28 (35.9%)	0.56
Dopamine	9 (7.6%)	4 (5.1%)	0.50
Dobutamine	10 (8.4%)	13 (6.7%)	0.08
Epinephrine	17 (14.3%)	10 (12.8%)	0.77

Abbreviations: COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; NE, norepinephrine; APACHE III, Acute Physiology and Chronic Health Evaluation III; SOFA, Sequential Organ Failure Assessment; SD, standard deviation.

Table 2 Primary and Secondary Outcomes

	Early Start	Late Start	*p* value
Primary outcome			
28-day mortality	43 (36.1%)	45 (57.7%)	<0.01
Secondary outcomes			
Hemodynamic response to vasopressin	74 (62.2%)	35 (44.9%)	0.02
Norepinephrine duration, hours	71.2±16.3	72.8±17.8	0.53
Vasopressin duration, hours	49.2±17.6	51.0±18.1	0.49
Mechanical ventilation-free days	11.9±11.2	8.4±9.9	0.03
CRRT-free days	13.2±12.0	9.5±10.3	0.03
Duration of ICU stays	7.7±4.6	8.9±6.2	0.10
Duration of hospital stays	10.6±6.7	12.0±9.7	0.23

Abbreviations: CRRT, continuous renal replacement therapy; ICU, intensive care unit.

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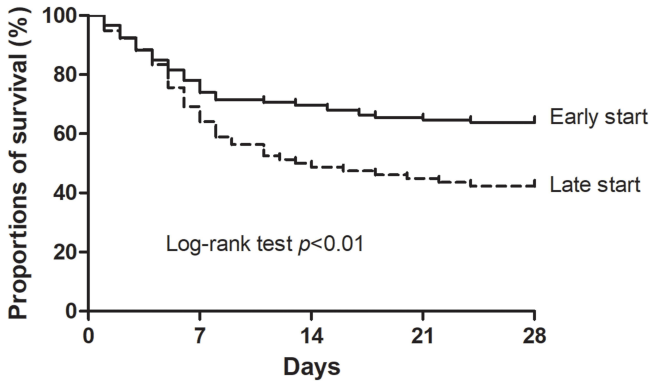

Figure 2 Kaplan–Meier curves for 28-day survival in older adults with septic shock, stratified by timing of vasopressin initiation The figure shows the cumulative probability of survival over 28 days for patients receiving early vasopressin (within 6 hours of norepinephrine initiation, n = 119, solid line) versus delayed vasopressin (6–72 hours after norepinephrine initiation, n = 78, dashed line). Survival differed significantly between groups (Log rank test, $p < 0.05$).

Secondary Outcomes

Patients receiving early vasopressin demonstrated a higher hemodynamic response rate (62.2% vs. 44.9%, $p = 0.02$). In terms of organ support, early initiation was associated with more mechanical ventilation-free days (11.9 ± 11.2 vs. 8.4 ± 9.9,

Table 3 Univariate and Multivariate Cox Regression for Exploring the Association of Vasopressin Start Time and 28-Day Mortality

	Univariate Analysis			Multivariate Analysis		
	HR	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Early start of vasopressin	0.56	0.37–0.85	<0.01	0.48	0.31–0.74	<0.01
Demographic						
Age	0.99	0.92–1.07	0.88			
Female	0.85	0.55–1.31	0.46			
Body mass index	1.04	0.92–1.18	0.53			
Comorbidities						
Diabetes mellitus	0.75	0.47–1.20	0.23			
Chronic heart failure	1.23	0.78–1.96	0.38			
COPD	0.98	0.60–1.62	0.95			
Chronic renal disease	0.82	0.47–1.40	0.46			
Liver disease	0.67	0.39–1.13	0.13			
Stroke	0.54	0.22–1.33	0.18			
Malignancy	1.33	0.79–2.23	0.29			
Scoring system						
APACHE III score	1.05	1.03–1.06	<0.01	1.05	1.03–1.06	<0.01
SOFA score	1.29	1.21–1.37	<0.01	1.26	1.19–1.35	<0.01
Characteristics at vasopressin initiation						
Mechanical ventilation	0.95	0.61–1.46	0.80			
CRRT	1.06	0.39–2.90	0.91			
NE dose	0.59	0.04–8.34	0.70			
Maximum lactate	0.93	0.76–1.16	0.53			
Medications						
Antibiotics	1.40	0.44–4.44	0.56			
Hydrocortisone	0.85	0.54–1.34	0.49			
Dopamine	0.98	0.43–2.24	0.96			
Dobutamine	1.74	0.99–3.03	0.05	0.79	0.45–1.39	0.42
Epinephrine	1.20	0.68–2.13	0.53			

Abbreviations: COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; NE, norepinephrine; APACHE III, Acute Physiology and Chronic Health Evaluation III; SOFA, Sequential Organ Failure Assessment; SD, standard deviation.

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$p = 0.03$) and continuous renal replacement therapy (CRRT)-free days (13.2 ± 12.0 vs. 9.5 ± 10.3, $p = 0.03$). The durations of norepinephrine (71.2 ± 16.3 vs. 72.8 ± 17.8 hours, $p = 0.53$) and vasopressin infusion (49.2 ± 17.6 vs. 51.0 ± 18.1 hours, $p = 0.49$) were similar between groups. Lengths of ICU stay (7.7 ± 4.6 vs. 8.9 ± 6.2 days, $p = 0.10$) and total hospital stay (10.6 ± 6.7 vs. 12.0 ± 9.7 days, $p = 0.23$) also did not differ significantly.

Discussion

In this study of older adults with septic shock, early initiation of vasopressin within six hours of norepinephrine commencement was associated with significantly lower 28-day mortality compared with delayed initiation. Moreover, early vasopressin use was associated with higher hemodynamic response and more days free from mechanical ventilation and CRRT, reflecting potential differences in circulatory recovery and organ function between groups.

Our findings are consistent with recent analyses supporting earlier vasopressin initiation in septic shock. In a multicenter study using public ICU databases, Sacha et al[19] reported that both higher norepinephrine-equivalent dose and longer delay from shock onset to vasopressin initiation were independently associated with increased in-hospital mortality, with an estimated 3% increase in risk per hour of delay. Similarly, Xu et al[20] demonstrated in the MIMIC-III and IV databases that vasopressin initiation at lower norepinephrine doses (<0.25 μg/kg/min) was associated with a 34% reduction in 28-day mortality. Additionally, White et al[16] found in an Australian cohort that vasopressin initiation within six hours of vasopressor therapy start significantly decreased hospital mortality (adjusted OR 0.69). Collectively, these studies underscore the potential harm of delayed vasopressin use, particularly when initiated at higher catecholamine doses or after prolonged hypotension. Nevertheless, evidence from previous literature has not been entirely consistent. Beck et al[21] found only a weak association between delayed vasopressor initiation and mortality, largely driven by extreme delays exceeding 14 hours. Such discrepancies likely reflect variations in illness severity, case mix, and definitions of "early" versus "late" initiation, as well as differences in sepsis management practices over time. Importantly, almost all prior studies investigated mixed-age adult populations, while older adults—who constitute the majority of septic shock cases—may have fundamentally distinct hemodynamic and hormonal responses. Age-related attenuation of vasopressin secretion, endothelial dysfunction, reduced β-adrenergic receptor sensitivity, and limited cardiac reserve may collectively heighten susceptibility to prolonged vasoplegia and catecholamine toxicity.[22] These pathophysiological features may explain why early vasopressin initiation confers a more pronounced benefit in older adults.

Mechanistically, timely vasopressin administration may restore vascular tone via non-catecholaminergic V1 receptor pathways before irreversible microcirculatory collapse develops.[23] By supplementing endogenous vasopressin deficiency early in the shock course, it can stabilize mean arterial pressure, reduce norepinephrine requirements, and minimize adrenergic myocardial stress.[24] For older adults, who often exhibit blunted autonomic compensation and increased sensitivity to adrenergic load, this early hemodynamic stabilization may be particularly critical to prevent secondary organ dysfunction.[25]

Clinically, our findings indicate that in older adults with septic shock, delayed vasopressin initiation was associated with worse outcomes despite comparable illness severity at baseline. It is important to note that at the time of vasopressin initiation, patients in the early group had higher norepinephrine requirements and lactate levels, reflecting potentially greater hemodynamic compromise. These observations suggest a potential association between earlier vasopressin administration—after adequate fluid resuscitation and initial norepinephrine support—and markers of improved circulatory stability, though causality cannot be established.[26] Such an approach is consistent with the concept of "early multimodal vasopressor support," aiming to restore vascular tone through complementary non-catecholaminergic mechanisms. Given the age-related alterations in cardiovascular responsiveness and baroreflex sensitivity, however, the optimal timing of vasopressin initiation in older adults warrants individualized assessment and further prospective validation.

Despite these insights, several limitations should be acknowledged. First, the retrospective observational design precludes causal inference, and residual confounding cannot be fully excluded despite adjustment for key clinical variables. Second, the definition of early versus delayed vasopressin initiation was based on a post-baseline exposure, which may introduce time-dependent (immortal time) bias, as patients in the delayed group were required to survive long enough to receive vasopressin. Although a uniform time-zero at norepinephrine initiation was applied and adjustments were made for disease severity at vasopressin initiation, this bias cannot be completely eliminated. Third, vasopressor initiation and overall hemodynamic management were not protocolized and relied on clinician judgment, raising the possibility of confounding by indication.

Similarly, fluid resuscitation strategies were not standardized, which may have contributed to variability in baseline severity and treatment timing. Fourth, the sample size was modest and the analysis focused on short-term outcomes, which may limit the generalizability of the findings. Larger prospective studies are warranted to validate these results. Finally, although missing data were limited, sensitivity analysis using multiple imputation yielded results consistent with the primary complete-case analysis, supporting the robustness of our findings. However, the potential impact of missing data cannot be entirely excluded.

Conclusion

In conclusion, early vasopressin initiation was associated with lower 28-day mortality and improved organ support–free days in older adults with septic shock. These findings suggest that the timing of vasopressin initiation may be an important factor in hemodynamic management in this high-risk population.

From a clinical perspective, earlier incorporation of vasopressin following adequate fluid resuscitation and initial norepinephrine therapy may be considered, particularly in patients with escalating vasopressor requirements. However, given the observational design, such strategies should be applied cautiously and individualized based on patient-specific conditions.

Future prospective studies, including those using time-dependent exposure models and incorporating geriatric-specific factors such as frailty, are needed to validate these findings and inform optimal vasopressor strategies in older adults.

Ethics Approval and Informed Consent

The study protocol was approved by the Institutional Review Board of Beijing Rehabilitation Hospital Affiliated to Capital Medical University (Approval No. 2024038). The study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was waived by the Institutional Review Board of Beijing Rehabilitation Hospital Affiliated to Capital Medical University due to the retrospective nature of the study and the use of de-identified data. All data were stored securely, and confidentiality was maintained throughout the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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