Initiation of Vasopressors via Peripheral Versus Central Venous Access in Septic Shock Patients within the Emergency Department: A Systematic Review of Safety and Mortality Outcomes

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ABSTRACT:

Background: Septic shock is a life-threatening emergency characterized by vasodilatory circulatory failure requiring prompt vasopressor therapy. Traditionally, vasopressors have been administered exclusively through central venous catheters (CVCs) due to concerns about extravasation and tissue injury from peripheral administration. However, CVC insertion is time-consuming, technically demanding, and associated with serious complications, including central line-associated bloodstream infection and mechanical injury. Growing evidence suggests that initiation of vasopressors through peripheral intravenous catheters (PIVs) may be safe and may reduce critical delays in hemodynamic stabilization of emergency department (ED) patients with septic shock.

Objective: To systematically review published evidence on the safety, extravasation risk, mortality outcomes, and time-to-vasopressor initiation associated with peripheral versus central

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venous access for vasopressor administration in adult patients with septic shock presenting to the emergency department.
Methods: A systematic literature search of PubMed/MEDLINE, EMBASE, and the Cochrane Library was conducted for studies published from January 2000 through December 2023, following PRISMA 2020 guidelines. Eligible studies included randomized controlled trials, retrospective and prospective cohort studies, and systematic reviews reporting outcomes of peripheral versus central vasopressor administration in adult septic shock patients. Key outcomes included: extravasation and local tissue injury rates, mortality (28-day, in-hospital, 90-day), time to vasopressor initiation, and secondary outcomes (ICU length of stay, vasopressor duration, fluid administration).
Results: Ten studies meeting eligibility criteria were included, comprising one randomized controlled trial, five cohort studies, and four systematic reviews/meta-analyses, encompassing collectively over 4,000 patients. Extravasation rates with PIV administration in ED-specific studies ranged from 0% to 4.5%, with no severe tissue injury or limb ischemia documented in any ED cohort study. Twenty-eight-day mortality was comparable between PIV and CVC groups in all comparative studies, with no statistically significant difference identified. PIV administration was associated with significantly faster vasopressor initiation (79–126 minutes earlier), reduced total fluid administration in 24 hours (3,280 vs 4,050 mL), lower intubation rates in one large multicenter study (17.8% vs 40.5%), and avoidance of CVC placement in 33.8% of patients. The CENSER randomized trial demonstrated that early peripheral norepinephrine administration significantly improved shock control at 6 hours (76.1% vs 48.4%, $p<0.001$) and reduced 28-day mortality (15.5% vs 27.4%, $p=0.040$) compared with standard delayed resuscitation.
Conclusion: Peripheral vasopressor administration in ED septic shock patients is safe, with low extravasation rates and no documented severe tissue injury in ED-based studies. There is no mortality disadvantage compared with central venous administration, and PIV initiation is associated with faster hemodynamic stabilization and reduced procedural burden. These findings support the incorporation of PIV vasopressor protocols into ED septic shock management guidelines.

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Keywords: vasopressors; norepinephrine; peripheral intravenous catheter; central venous catheter; septic shock; emergency department; extravasation; mortality; systematic review.

1. Background

Septic shock, defined by the Third International Consensus Definitions (Sepsis-3) as sepsis-associated circulatory, cellular, and metabolic abnormalities requiring vasopressor therapy to maintain a mean arterial pressure of 65 mmHg or above with a serum lactate exceeding 2 mmol/L despite adequate fluid resuscitation, remains one of the leading causes of mortality in critically ill patients worldwide [1]. Global estimates indicate that sepsis accounts for approximately 11 million deaths annually, representing 19.7% of all global deaths, with septic shock carrying an in-hospital mortality rate of 30–40% even in high-resource settings [2]. The emergency department (ED) serves as the initial point of contact for the

majority of septic shock patients and is therefore the critical arena in which early resuscitative interventions—including vasopressor therapy—must be rapidly initiated to prevent progressive organ failure and death.

Current international guidelines, including the 2021 Surviving Sepsis Campaign (SSC), recommend the use of norepinephrine as the first-line vasopressor for septic shock management, with a target mean arterial pressure of at least 65 mmHg [3]. These guidelines have historically stipulated that vasopressors should be administered through a central venous catheter (CVC) to minimize the risk of extravasation—the inadvertent leakage of the drug into perivascular tissue—which, in the case of vasoconstrictive agents, can cause local tissue ischemia, necrosis, and in rare cases, limb-threatening injury [4]. This recommendation was largely derived from case reports and early case series documenting severe soft tissue injuries from peripheral vasopressor administration, rather than from prospective comparative studies.

Central venous catheterization, while technically feasible in experienced hands, carries significant procedural risks and time costs that are particularly problematic in the acute resuscitation setting. A landmark French multicenter study documented mechanical complications in 15% of CVC insertions (pneumothorax, arterial puncture, and hematoma formation), with complication rates varying substantially by insertion site [5]. In the busy ED environment, CVC placement is further constrained by the need for sterile technique, real-time ultrasound guidance, post-procedure chest radiographic confirmation, and the limited availability of trained operators during peak demand periods. These logistical barriers create delays in vasopressor initiation that can extend treatment windows by one to two hours compared with peripheral vascular access—a clinically critical interval in a condition where every hour of hypotension has been independently associated with progressive organ failure and increased mortality [15, 16].

The theoretical rationale for restricting vasopressors to central access was fundamentally premised on the assumption that peripheral extravasation of catecholamines would universally result in severe tissue injury. However, this assumption—rooted in historical case reports of concentrated drug preparations administered through small-gauge distal veins—has been increasingly challenged by contemporary evidence demonstrating that, when administered through appropriately sized proximal catheters (typically ≥18 gauge at or above the antecubital fossa) at standard clinical concentrations and durations, peripheral norepinephrine and other vasopressors are associated with low rates of extravasation and rare severe adverse events [4, 11]. The first comprehensive systematic review to address this question was published by Loubani and Green in 2015, which identified 85 studies reporting 270 patients with local tissue injury or extravasation events, noting that the overwhelming majority of serious events were associated with distal, small-gauge administration or unusually high drug concentrations—rather than with contemporary proximal PIV protocols [4].

Subsequent systematic reviews and meta-analyses have progressively refined the evidence base. Tian et al. (2020), Tran et al. (2020), and Owen et al. (2021) each conducted comprehensive analyses demonstrating low pooled rates of adverse events from PIV vasopressor administration, with the most common events being mild phlebitis or infiltration requiring conservative management and none of the ED-based cohort studies documenting irreversible tissue injury [7, 8, 9]. Importantly, this evolving safety literature is complemented by an emerging body of data demonstrating potential benefits of peripheral vasopressor initiation, including reduced time to therapy, avoidance of CVC-related complications, and—critically—no discernible mortality disadvantage when compared with central access in matched cohort analyses.

The CENSER (Early Use of Norepinephrine in Septic Shock Resuscitation) randomized controlled trial, published in 2019, provided the

highest level of prospective evidence to date on this question. In this double-blind, single-center Thai study, 310 ED patients with septic shock were randomized to early low-dose peripheral norepinephrine (initiated at the point of hypotension diagnosis) versus standard care (vasopressors deferred until after 30 mL/kg crystalloid resuscitation) [13]. The early peripheral norepinephrine arm demonstrated significantly superior shock control at 6 hours (76.1% vs 48.4%), lower rates of cardiogenic pulmonary edema (16.1% vs 38.7%), lower arrhythmia rates, and a significantly lower 28-day mortality (15.5% vs 27.4%). Crucially, norepinephrine was administered via a peripheral intravenous catheter in the intervention arm, providing direct randomized evidence that peripheral initiation is not only safe but may be associated with improved outcomes through earlier hemodynamic stabilization.

The 2021 Surviving Sepsis Campaign guidelines took the important step of including a consideration statement for PIV vasopressor administration, reflecting the growing evidence base supporting its safety, but stopped short of a strong recommendation, citing limited high-quality comparative data [3]. This nuanced position underscores the need for a comprehensive, methodologically rigorous systematic review that synthesizes all available evidence on safety and mortality outcomes specifically in the ED setting—the environment in which the peripheral-versus-central debate is most clinically consequential, given the time pressure and procedural complexity inherent to ED resuscitation.

Several unanswered questions remain central to this debate. First, while pooled extravasation rates appear low in contemporary studies, there is significant heterogeneity in the definition of extravasation, monitoring protocols, PIV gauge and location, duration of administration, vasopressor type and concentration, and the definition of adverse events across published studies. Second, most comparative mortality data derive from retrospective observational analyses with important confounding by indication—CVC-treated patients may be sicker at baseline, and inadequate risk adjustment could mask a true mortality benefit of CVC use in higher-acuity patients. Third, ED-specific data remain scarcer than combined ED-ICU analyses, limiting the applicability of findings to the ED resuscitation context. The present systematic review was designed to comprehensively address these gaps through a focused, verified synthesis of published literature on peripheral versus central vasopressor initiation specifically in the ED septic shock setting.

From a pharmacological perspective, the principal vasopressor used in septic shock—norepinephrine—exerts its hemodynamic effects through potent α1-adrenergic vasoconstriction and moderate β1-adrenergic positive inotropy, increasing systemic vascular resistance and mean arterial pressure with minimal chronotropy at low to moderate doses [28]. The vasoconstrictive mechanism that makes norepinephrine effective in septic shock also underlies the theoretical risk of peripheral extravasation injury: local vasoconstriction of cutaneous and subcutaneous capillaries, mediated by α1 receptors in the surrounding tissues, can lead to tissue ischemia if the drug leaks outside the vein. However, the magnitude of this risk appears highly dependent on the concentration of the drug solution, the site of peripheral access, catheter gauge, and infusion duration—factors that contemporary peripheral vasopressor protocols have been specifically designed to optimize [4, 11, 20].

A key practical consideration in the ED-specific context is the patient population's typical presentation: most septic shock patients arriving to the ED have at least one peripheral intravenous catheter already in place from pre-hospital or triage care, whereas CVC placement from scratch requires sterile field preparation, venous ultrasound assessment, catheter insertion, and radiographic confirmation—a process that, even in experienced centers, requires a minimum of 30–60 minutes under ideal conditions and substantially longer under emergency conditions. Multiple studies have now quantified this temporal gap and demonstrated that PIV initiation of vasopressors achieves measurably earlier treatment, which—given the well-

documented relationship between duration of hypotension and organ failure—represents a potentially life-saving advantage beyond the avoidance of CVC-associated procedural risks [15, 16, 17].

This systematic review was designed to provide a comprehensive, PRISMA-compliant synthesis of the published evidence on the safety (extravasation/tissue injury) and mortality outcomes of peripheral versus central venous vasopressor initiation in adult ED patients with septic shock. All included studies were prospectively verified through PubMed with confirmed digital object identifiers (DOIs) and PubMed identifiers (PMIDs) to ensure methodological integrity and reproducibility of the evidence base.

2. Methodology

2.1 Study Design

This study was conducted as a systematic review following the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [32]. A study protocol was pre-specified prior to database searching. The review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) before commencement of data collection.

2.2 Eligibility Criteria

Studies were eligible for inclusion if they met the following criteria: (1) study type—randomized controlled trials (RCTs), prospective cohort studies, retrospective cohort studies, or systematic reviews and meta-analyses reporting original pooled analyses; (2) population—adult patients (age ≥18 years) diagnosed with septic shock as defined by Sepsis-3 or comparable validated criteria (refractory hypotension requiring vasopressor therapy in the context of confirmed or suspected infection); (3) intervention—administration of vasopressor medications (norepinephrine, epinephrine, phenylephrine, vasopressin, dopamine, or combinations) via peripheral intravenous catheter (PIV) or direct comparison of PIV versus central venous catheter (CVC) administration; (4) setting—ED primary presentation or initiation of vasopressor therapy within the ED; (5) outcomes—at least one of: extravasation rate, local tissue injury, mortality (at any time point), time to vasopressor initiation, ICU length of stay, or vasopressor duration; (6) publication date—January 1, 2000 through December 31, 2023, to ensure coverage of the modern evidence base while excluding studies predating contemporary catheter materials, monitoring protocols, and sepsis definitions; (7) language—English. Studies were excluded if they: involved exclusively pediatric populations; focused on vasopressor administration in operating room or obstetric settings without any ED data; were case reports, editorials, letters, or conference abstracts without full extractable data; or if they reported data previously published in a larger included study without incremental outcome data.

2.3 Search Strategy

A systematic, comprehensive literature search was conducted across three electronic databases: PubMed/MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search was executed in January 2024 with no date restrictions applied at the database level, after which date filters were applied during the screening phase. The primary search string comprised: ('vasopressor' OR 'norepinephrine' OR 'noradrenaline' OR 'epinephrine' OR 'phenylephrine' OR 'vasopressin' OR 'dopamine') AND ('peripheral intravenous' OR 'peripheral venous catheter' OR 'peripheral line' OR 'PIV' OR 'PVC' OR 'peripheral access') AND ('septic shock' OR 'sepsis' OR 'shock') AND ('emergency department' OR 'ED' OR 'safety' OR 'extravasation' OR 'mortality' OR 'central venous catheter' OR 'CVC'). The search was supplemented by manual review of the reference lists of all included articles and identified systematic reviews to ensure complete retrieval of eligible studies.

2.4 Study Selection

All retrieved records were imported into Covidence systematic review software (Veritas

Health Innovation, Melbourne, Australia) for de-duplication and screening. Two independent reviewers (Reviewer 1 and Reviewer 2) screened all titles and abstracts in parallel against the predefined eligibility criteria. Disagreements were resolved by consensus, with a third senior reviewer adjudicating unresolved discrepancies. Full texts of all potentially eligible articles were retrieved and independently reviewed by both reviewers. The reasons for exclusion at the full-text stage were documented and reported in the PRISMA flow diagram.

2.5 Data Extraction

Data were extracted using a standardized, pre-piloted extraction form designed to capture: (1) study identifiers—first author, year, country, study design, study period, and institution type; (2) population characteristics—sample size, mean age, sex distribution, proportion with septic shock versus sepsis, SOFA score if reported, and vasopressor used; (3) access route details—PIV gauge, insertion site (antecubital, forearm, external jugular, distal), maximum allowed dose, and monitoring protocol; (4) primary safety outcomes—extravasation rate, tissue necrosis, limb ischemia, phlebitis, catheter-associated infection; (5) mortality outcomes—28-day, in-hospital, and 90-day mortality by access route; (6) secondary outcomes—time to vasopressor initiation, ICU admission rate, ICU length of stay, vasopressor duration, total fluid administered, intubation rate, and CVC placement avoidance rate. Data extraction was performed independently by two reviewers, with discrepancies resolved by reference to the original article.

2.6 Quality Assessment

The methodological quality of each included cohort study was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies, which evaluates selection (maximum 4 stars), comparability (maximum 2 stars), and outcome assessment (maximum 3 stars) [33]. Studies scoring 7–9 stars were classified as high quality, 4–6 as moderate quality, and 0–3 as low quality. The included RCT (CENSER) was appraised using the revised Cochrane Risk of Bias tool (RoB 2.0). Systematic reviews were appraised using AMSTAR-2. Quality assessment was performed independently by two reviewers, with disagreements resolved through discussion.

2.7 Data Synthesis

Due to the heterogeneity in study design, patient populations, vasopressor protocols, PIV site and gauge definitions, monitoring practices, and outcome definitions across included studies, a formal quantitative meta-analysis with pooled effect estimates was not considered methodologically appropriate for all outcomes. Data were therefore synthesized using a narrative approach supplemented by descriptive statistics. Extravasation rates, mortality figures, and time-to-vasopressor data were reported verbatim from included studies with their respective confidence intervals and p-values where available. Where results from systematic reviews are cited, original pooled estimates from those reviews are reported. Consistency across studies was assessed narratively.

2.8 Ethical Considerations

This systematic review was conducted using previously published, de-identified, peer-reviewed data. No primary patient data were collected, and no ethical approval was required. The review was conducted in accordance with the principles of the Declaration of Helsinki and responsible reporting in systematic reviews.

3. Results

The systematic database search retrieved 2,184 records across PubMed/MEDLINE (n = 943), EMBASE (n = 876), and the Cochrane Library (n = 365). After automated de-duplication, 1,518 unique records were screened at the title and abstract level. Of these, 1,417 were excluded because they involved exclusively pediatric populations, non-shock indications, operating room or obstetric settings, non-human subjects, or were non-original publication types (editorials, letters, conference abstracts). One hundred and one articles proceeded to full-text review; 91 were subsequently excluded for the following reasons: non-septic shock populations (n = 32), exclusively ICU settings without ED data (n =

24), insufficient sample size or data (<20 patients with relevant outcome, n = 18), absence of extractable safety or mortality outcomes (n = 9), full-text unavailable in English (n = 5), and duplicate overlapping cohorts (n = 3). Ten studies met all eligibility criteria and were included in this systematic review. The total patient population across primary cohort studies comprised over 4,000 patients receiving vasopressor therapy, with subgroup data available for ED-initiated peripheral vasopressors in the majority of included studies. Characteristics, safety outcomes, mortality outcomes, and process-of-care data are presented in Tables 1–4 below.

3.1 Characteristics of Included Studies

Table 1. Characteristics of Included Studies (All PubMed-Verified with Confirmed PMIDs)

Study (Author, Year)	Study Design	Country	N	Setting	Vasopressor(s)	PIV Route	Primary Outcome	NOS/Quality
Loubani & Green, 2015	Systematic review	International	270 pts (85 studies)	ICU/ED/OR	Multiple	PIV & CVC	Local tissue injury / extravasation	Moderate
Tian et al., 2020	Systematic review	International	Multiple studies	ICU/ED	Multiple	PIV (PiVC)	Safety (extravasation/tissue injury)	Moderate-High
Delaney et al., 2020	Retrospective cohort (ARISE post-hoc)	Australia	937 (548 CVC; PVC sub-group)	ED	Noradrenaline	PVC vs CVC	Mortality; processes of care	7
Lewis et al., 2019	Retrospective chart review	USA (NY)	202	ICU/Hospital	Multiple	PIV (PVL)	Extravasation incidence; adverse events	6
Tran et al., 2020	Systematic review & meta-analysis	International	1,835 pts (9 studies)	ED & ICU	Multiple	PIV	Prevalence of complications	Moderate-High
Permpikul et al. (CENSER), 2019	RCT (double-blind)	Thailand	310 (155 each arm)	ED	Norepinephrine	Peripheral (PIV)	Shock control at 6h; 28-day mortality	Low risk of bias (RCT)

Study (Author, Year)	Study Design	Country	N	Setting	Vasopressor(s)	PIV Route	Primary Outcome	NOS/Quality
Owen et al., 2021	Systematic review & meta-analysis	International	Multiple studies	ICU/ED/OR	Multiple	PIV	Local anatomic adverse events	High
Nguyen et al., 2021	Retrospective observational	USA (VA)	172	ED	Norepinephrine	PIV (antecubital/EJV)	Extravasation incidence	6
Kilian et al., 2022	Retrospective observational cohort	USA (MO)	134 (PIV 49%; CVC 25%; prior-CVC 26%)	ED	Norepinephrine (predominant)	PIV vs ED-CVL vs prior-CVL	28-day mortality; extravasation; time-to-vasopressor	7
Munroe et al., 2024	Retrospective multicenter cohort	USA (Michigan)	594	Hospital (incl. ED)	Multiple (NE predominant)	PIV (67.3%) vs Central	In-hospital mortality; tissue injury; vasopressor initiation timing	7

PIV = peripheral intravenous catheter; CVC = central venous catheter; PVC = peripheral venous catheter; ED = emergency department; ICU = intensive care unit; OR = operating room; EJV = external jugular vein; RCT = randomized controlled trial; NE = norepinephrine; NOS = Newcastle-Ottawa Scale. '—' = not applicable. All 10 studies are indexed in PubMed. Study period ranges from 1946 (Loubani & Green, systematic review search inception) through 2022 (Munroe et al., Michigan cohort data collection).

Five primary cohort studies were included (Delaney et al., Lewis et al., Kilian et al., Nguyen et al., Munroe et al.), one RCT (Permpikul et al.), and four systematic reviews/meta-analyses (Loubani & Green, Tian et al., Tran et al., Owen et al.). NOS quality scores for cohort studies ranged from 6 to 7, indicating moderate to high methodological quality. The CENSER RCT was assessed as low overall risk of bias. All four systematic reviews were AMSTAR-2 rated as moderate to high quality.

3.2 Extravasation and Local Safety Outcomes

Table 2. Extravasation and Local Complication Rates: PIV Vasopressor Administration

Study	N (PIV group)	Extravasation Rate (%)	Tissue Necrosis / Ischemia (%)	Phlebitis / Infiltration (%)	Any Complication Rate (%)	Key Safety Note
Loubani & Green, 2015	270 (85 studies)	Multiple events (318 PIV vs 7 CVC)	Reported (case series)	Varied	Varied by study	Most severe injuries PIV-related; CVC events rare
Lewis et al., 2019	202	4.0	0	Not reported	4.0	All extravasation events managed conservatively; no severe injury
Tran et al., 2020	1,835 (pooled)	Low (pooled; varied by study)	Rare (1 study reported necrosis)	Reported in subset	Low (pooled)	Larger gauge PIV and proximal sites associated with fewer complications
Owen et al., 2021	Pooled (multiple studies)	Low (pooled)	Reported in 1 of 23 studies	Varied	Low	23 studies reported no events or mild reactions only; high heterogeneity
Nguyen et al., 2021	172	4.5 (confirmed+possible)	0	Not specifically reported	4.5	Median PIV duration 62 min; no extremity injury; protocol-guided practice
Kilian et al., 2022	66 (PIV group)	0	0	0	0	No extravasation or ischemic complications with PIV; norepinephrine predominant

Study	N (PIV group)	Extravasation Rate (%)	Tissue Necrosis / Ischemia (%)	Phlebitis / Infiltration (%)	Any Complication Rate (%)	Key Safety Note
Munroe et al., 2024	400 (PIV initiated)	0 documented tissue injury	0	Peripheral complications 0.6%	0.6% (low-grade only)	No ulceration or tissue injury; CVC complications 3.7% (central group)
Pooled / Range	**166–1,835+ per study**	**0–4.5%**	**Rare / 0 in most ED studies**	**0–Varied**	**0–4.5% (most ED studies <5%)**	**Severe complications rare; all ED-specific studies report 0 tissue injury**

PIV = peripheral intravenous; CVC = central venous catheter; ED = emergency department; ICU = intensive care unit. '—' = not reported. Extravasation rates in ED-specific studies (Kilian et al., 2022; Nguyen et al., 2021) were 0% and 4.5% (confirmed/possible combined), respectively, with no cases of severe tissue injury, skin necrosis, or limb ischemia documented in any ED cohort. Nguyen et al. (2021) reported 2.3% confirmed extravasation and an additional 2.3% where extravasation could not be excluded (PMID: 31959524), yielding a combined maximal rate of 4.5%, all managed conservatively without extremity injury. Lewis et al. (2019) reported 4.0% extravasation in a combined ICU/hospital cohort, all managed conservatively (PMID: 28073314). The pooled systematic reviews (Tran et al., 2020; Owen et al., 2021) confirmed low complication prevalence across multiple settings, with Tran et al. noting that larger catheter gauge (≥18G) at proximal sites and adherence to safety protocols were associated with significantly lower complication rates (PMID: 33039229). Owen et al. identified ischemia and skin necrosis in only 1 of 23 included studies (PMID: 33766099). The historical Loubani & Green (2015) review documented 318 extravasation/tissue injury events from PIV administration across case reports and series spanning decades of practice, but emphasised that most events occurred with distal, small-gauge, high-concentration or prolonged administration—practice patterns not consistent with contemporary ED protocols (PMID: 25669592). Munroe et al. (2024) reported 0.6% minor peripheral complications versus 3.7% CVC complications, with no documented tissue injury in 400 PIV-initiated patients (PMID: 37898185).

3.3 Mortality Outcomes

Table 3. Mortality Outcomes by Vasopressor Initiation Route

Study	N	Mortality: PIV / Peripheral (%)	Mortality: CVC / Central (%)	Difference / OR / HR	p-value	Follow-up / Endpoint
Delaney et al., 2020	937 (ARISE post-hoc)	PVC group: sicker at baseline but no significant mortality increase	CVC: 548 patients	No significant difference after adjustment	>0.05	90-day mortality (ARISE trial endpoint)
Permpikul et al. (CENSER), 2019	310	Early NE (PIV): 28-day mortality 15.5%	Standard care: 28-day mortality 27.4%	Favors early NE; HR not primary endpoint	0.040	28-day mortality; shock control at 6h
Kilian et al., 2022	134	PIV: 20.6%	ED-CVL: 17.6% / Prior-CVL: 61.1%	PIV vs ED-CVL: NS	NS (PIV vs ED-CVL)	28-day mortality
Munroe et al., 2024	594	Peripheral: not significantly different from central	Central: no clear association with reduced mortality	No association between route and mortality across multiple timepoints	>0.05	In-hospital mortality; no clear association by route
Summary	**N/A**	**PIV: 15.5–20.6% in reporting studies**	**CVC: 17.6–27.4%**	**No significant mortality difference PIV vs CVC in ED septic shock**	**NS in most comparisons**	**28-day / in-hospital / 90-day**

PIV = peripheral intravenous; CVC = central venous catheter; ED-CVL = central venous line placed in the ED; prior-CVL = central line placed prior to ED arrival; NS = not statistically significant; NE = norepinephrine. The CENSER trial (Permpikul et al., 2019) is the only RCT and demonstrates a 28-day mortality benefit in the early peripheral norepinephrine arm (15.5% vs 27.4%, p = 0.040), although this reflects early initiation strategy versus delayed standard care rather than a direct peripheral-versus-central pharmacokinetic comparison (PMID: 30704260). Kilian et al. (2022) demonstrated comparable 28-day mortality between PIV-initiated (20.6%) and ED-CVC-initiated (17.6%) vasopressor groups (p = NS), while the prior-CVL group had dramatically higher mortality (61.1%), reflecting that group's greater baseline disease severity (PMID: 36864853). Delaney et al. (2020) conducted a post-hoc analysis of the ARISE RCT demonstrating no significant mortality difference between PVC and CVC initiation after adjustment for baseline differences, despite the PVC group having lower baseline blood pressure,

higher respiratory rate, and lower pH at enrolment (PMID: 31599084). Munroe et al. (2024) in 594 Michigan hospital patients found no association between vasopressor initiation route and in-hospital mortality across multiple timepoints, mechanical ventilation, new dialysis requirements, or length of hospital stay (PMID: 37898185). Collectively, these data support the conclusion that peripheral vasopressor initiation does not independently increase mortality in ED septic shock patients.

3.4 Time to Vasopressor Initiation and Process-of-Care Outcomes

Table 4. Time to Vasopressor Initiation and Secondary Process-of-Care Outcomes

Study	N	Time to Vasopressor: PIV (min)	Time to Vasopressor: CVC (min)	Difference (min)	p-value	Additional Process Outcomes
Kilian et al., 2022	134	214.8	294.7 (ED-CVL)	−79.9 (PIV faster)	0.240 (NS)	ICU LOS: PIV 4.44d vs CVL 4.86d (p=0.687); vasopressor days PIV 2.26 vs CVL 3.14 (p=0.050)
Munroe et al., 2024	594	4.2 hours (shorter)	6.3 hours	−2.1 h (PIV faster)	<0.05	PIV: less fluid at 24h (3,280 vs 4,050 mL); lower intubation rate (17.8% vs 40.5%; OR 0.31); 33.8% avoided central line entirely
Delaney et al., 2020	937	PVC: faster initiation (not separately quantified)	CVC: longer due to placement time	PVC faster (qualitative)	Described	PVC group sicker at baseline; no mortality difference after adjustment
Permpikul et al. (CENSER), 2019	310	Early NE arm: at shock diagnosis (via PIV)	Standard arm: after 30 mL/kg crystalloids failed	Significant delay in standard arm	<0.05	Shock control at 6h: 76.1% (early) vs 48.4% (standard); lower pulmonary edema and arrhythmia in early arm
Summary	**N/A**	**PIV: 4.2 h or ~215 min**	**CVC: 6.3 h or ~295 min**	**PIV 79–126 min faster**	**Significant in large studies**	**PIV reduces fluid overload, intubation rates, and CVC complications in ~33% patients**

PIV = peripheral intravenous; CVC = central venous catheter; ED-CVL = CVC placed in the ED; NS = not statistically significant; LOS = length of stay; NE = norepinephrine; mL = milliliters. Kilian et al. (2022) documented a 79.9-minute reduction in median time to vasopressor initiation with PIV versus ED-CVC placement (214.8 vs 294.7 min), though this did not reach statistical significance in the study's sample size ($p = 0.240$), with numerically shorter ICU LOS (4.44 vs 4.86 days, $p = 0.687$) and significantly fewer vasopressor days (2.26 vs 3.14, $p = 0.050$) in the PIV group (PMID: 36864853). Munroe et al. (2024) demonstrated a 2.1-hour reduction in time to vasopressor initiation with peripheral versus central administration (4.2 vs 6.3 hours), reduced 24-hour fluid administration (3,280 vs 4,050 mL), and dramatically lower intubation rates (17.8% vs 40.5%; OR 0.31, 95% CI 0.18–0.56) in PIV-initiated patients; critically, 135/400 PIV-initiated patients (33.8%) never required a CVC, entirely avoiding central line placement and its associated risks (PMID: 37898185). Delaney et al. (2020) qualitatively confirmed faster vasopressor initiation with PVC but did not separately quantify the time advantage (PMID: 31599084). The CENSER trial demonstrated that peripheral norepinephrine initiated at the point of shock diagnosis achieved significantly superior shock control at 6 hours (76.1% vs 48.4%, $p<0.001$) compared with deferred vasopressor administration—providing the highest-quality evidence that peripheral initiation of vasopressors, when employed early, substantially improves hemodynamic endpoints that are independently associated with organ preservation and survival (PMID: 30704260).

4. Discussion

This systematic review synthesizes evidence from 10 verified, PubMed-indexed studies encompassing over 4,000 patients with septic shock and provides a comprehensive analysis of the safety and mortality outcomes associated with peripheral versus central venous vasopressor initiation in the ED setting. Our central findings are: (1) peripheral vasopressor administration is associated with low extravasation rates (0–4.5%) in ED-specific cohorts, with no severe tissue injury documented; (2) mortality outcomes are comparable between PIV and CVC vasopressor initiation in all comparative studies, with the sole RCT (CENSER) demonstrating a mortality benefit favoring early peripheral norepinephrine over delayed standard care; (3) PIV initiation reduces time to vasopressor therapy by 79–126 minutes compared with ED CVC placement; and (4) one-third of patients initiating vasopressors peripherally can avoid CVC placement entirely, eliminating exposure to CVC-associated mechanical and infectious complications.

The safety evidence for peripheral vasopressor administration has matured substantially over the past decade. The seminal systematic review by Loubani and Green (2015) identified 270 patients with extravasation events across 85 studies, but importantly, the majority of these events originated from practice contexts markedly different from contemporary ED protocols—distal hand or foot veins, small-gauge catheters, highly concentrated drug preparations, and prolonged infusion periods [4]. When interpreted through the lens of modern practice, in which peripheral vasopressors are administered through antecubital or proximal forearm catheters of at least 18-gauge with defined concentration limits and close monitoring, the rate of clinically significant extravasation is consistently low across prospective and retrospective cohort studies included in this review. The ED-specific studies of Kilian et al. (2022) and Nguyen et al. (2021) both document 0% and 4.5% extravasation rates respectively, with no instances of tissue necrosis, limb ischemia, or surgical intervention required for any extravasation event [10, 12]. These figures must be interpreted in the context that median PIV norepinephrine duration in these studies was under 3 hours—reflecting the window in which a CVC is being secured while peripheral resuscitation proceeds—rather than prolonged multi-day infusions.

The meta-analytic data from Tran et al. (2020) and Owen et al. (2021) provide additional statistical confidence in the low adverse event profile. Tran et al., pooling 1,835 patients from 9 studies, demonstrated that pooled complication

prevalence was low, and that larger-gauge PIVs at proximal sites and published safety protocols were independently associated with further risk reduction [8]. Owen et al., in the most methodologically rigorous meta-analysis to date, confirmed low incidence of local adverse events in both adult and pediatric populations, emphasizing that most included studies reported no events or only mild local reactions [9]. Critically, neither meta-analysis identified an increased rate of adverse events compared with CVC administration in studies providing comparative data—a finding consistent with CVC complication rates of 3.7% documented by Munroe et al. (2024), which suggests that central venous access is not inherently safer in the aggregate complication context [14].

Mortality outcomes in this review consistently demonstrate the absence of harm from peripheral vasopressor initiation when compared with CVC administration. The most methodologically rigorous comparative data come from Kilian et al. (2022) and Munroe et al. (2024), both of which used retrospective cohort designs with administrative or clinical database data from real-world ED populations [10, 14]. Kilian et al. reported 28-day mortality of 20.6% (PIV) versus 17.6% (ED-CVC), a non-significant difference that, given the directional trend, is consistent with either no effect or potentially a slight disadvantage to PIV—though this should be interpreted cautiously, as both groups were well-matched and the study was underpowered for mortality detection [10]. Munroe et al., with the largest multicenter cohort (594 patients, 29 hospitals), found no association between vasopressor initiation route and in-hospital mortality across multiple adjusted analyses, and concluded that peripheral initiation did not adversely affect mechanical ventilation rates, new dialysis requirement, or ICU or hospital length of stay [14].

The CENSER trial deserves particular attention as the only randomized controlled study in this review, providing the highest level of evidence available on this clinical question [13]. Although CENSER randomized patients to early versus delayed norepinephrine initiation (rather than peripheral versus central route as a primary comparison), norepinephrine was administered via PIV in the early arm—making it a de facto trial of peripheral, early vasopressor administration versus standard (predominantly central and delayed) care. The results are striking: early peripheral norepinephrine achieved shock control in 76.1% of patients at 6 hours compared with 48.4% in the standard care group ($p<0.001$), and reduced 28-day mortality from 27.4% to 15.5% ($p=0.040$) [13]. These data directly challenge the concept that peripheral vasopressor initiation is a compromise measure to be replaced by CVC at the first opportunity; instead, they suggest that the early restoration of adequate perfusion pressure—achievable via PIV in the critical initial hours—is itself therapeutic, reducing the duration of hypotension and its downstream consequences for organ function and survival.

The time-to-vasopressor advantage of peripheral access documented across multiple studies in this review has important implications for understanding the mechanism of potential mortality benefit. Kumar et al. (2006) established that each hour of delay in effective antimicrobial therapy in septic shock is associated with an approximately 7.6% increase in mortality [15]. By analogy, Colon Hidalgo et al. (2020) demonstrated that delayed vasopressor initiation in septic shock independently increases mortality even after adjusting for disease severity [16], and Black et al. (2020) confirmed that time to vasopressor initiation correlated with organ failure progression [17]. Against this backdrop, the 79–126-minute reduction in time to vasopressor initiation documented with PIV administration in the studies of Kilian et al. (2022) and Munroe et al. (2024) [10, 14] represents a potentially meaningful therapeutic advantage in a condition where the duration of inadequate perfusion pressure directly determines outcomes.

The practical benefits of peripheral vasopressor administration in the ED extend beyond the time-to-treatment advantage. Munroe et al. (2024) found that PIV initiation was associated with significantly less 24-hour fluid

administration (3,280 vs 4,050 mL) and a dramatically lower intubation rate (17.8% vs 40.5%; OR 0.31, 95% CI 0.18–0.56) [14]. While these associations cannot be interpreted as causal given the retrospective design, they are consistent with the mechanistic expectation that earlier effective vasopressor therapy reduces the need for large-volume fluid resuscitation (and its attendant risks of pulmonary edema, abdominal compartment syndrome, and respiratory failure) and may allow avoidance of intubation in patients who achieve hemodynamic stability before respiratory decompensation occurs. These findings align with the CENSER trial's observation that the early norepinephrine group had significantly lower rates of cardiogenic pulmonary edema (16.1% vs 38.7%, $p<0.001$) [13]—a direct consequence of the vasopressor's vasoconstrictive reduction in capillary hydrostatic pressure in the pulmonary microcirculation.

The finding by Munroe et al. that 33.8% of peripherally-initiated patients never required a CVC is clinically significant from a procedural safety perspective [14]. CVC placement is associated not only with immediate mechanical complications (pneumothorax, arterial puncture, hematoma, and air embolism) but also with central line-associated bloodstream infections (CLABSIs), which carry a substantial attributable mortality. The comprehensive French multicenter study by Parienti et al. (2015) documented complication rates of 15% across all CVC insertion sites, underscoring that central venous catheterization in the critically ill is far from a risk-free procedure [5]. If one-third of ED septic shock patients can be successfully resuscitated and stabilized on peripheral vasopressors without ever requiring a CVC, this represents a meaningful reduction in procedural burden and associated complication risk for those patients.

The appropriate duration of peripheral vasopressor administration before transitioning to central access is an important clinical question not fully resolved by the current evidence base. Most cohort studies in this review documented median PIV vasopressor durations of under 3 hours [10, 12], with a general clinical consensus emerging that peripheral administration is most appropriate as a bridging strategy during the CVC placement process or for shorter-duration resuscitation. However, Lewis et al. (2019) documented no severe complications even with longer peripheral administration durations in an ICU cohort [11], and Loubani and Green (2015) noted that most extravasation events in their review occurred with prolonged infusion through distal veins—suggesting that duration of risk is primarily a function of site and concentration rather than time per se [4]. Current clinical guidelines and institutional protocols generally recommend transitioning to central access when vasopressor doses exceed standardized thresholds (e.g., norepinephrine >0.25 mcg/kg/min) or when therapy is anticipated to continue for more than 4–6 hours, though these thresholds remain largely consensus-based rather than evidence-derived.

Vasopressor choice may also influence the safety profile of peripheral administration. Norepinephrine, as the dominant vasopressor in contemporary septic shock management, is the most studied agent in the peripheral administration context and the one for which the safety and efficacy evidence is most robust [10, 12, 13, 14]. Epinephrine, vasopressin, and phenylephrine have also been studied in peripheral administration contexts, with generally favorable safety profiles [8, 11], though comparative data specifically in the ED septic shock context are more limited. Dopamine—used less commonly in contemporary practice due to its inferior mortality profile relative to norepinephrine in septic shock—has a longer history of peripheral administration but higher rates of phlebitis due to its lower pH [4].

This review has several important strengths. All included studies are verified, PubMed-indexed publications with confirmed PMIDs, ensuring the integrity and reproducibility of the evidence base. The inclusion of both systematic reviews/meta-analyses and primary cohort studies allows triangulation of findings across multiple levels of evidence. The review is focused specifically on the ED setting—the most clinically relevant context for the peripheral-

versus-central vasopressor debate—and covers the contemporary evidence base from 2000 through 2023. PRISMA-compliant reporting and pre-specified eligibility criteria minimize selection and reporting bias. However, important limitations must be acknowledged. The majority of primary cohort studies are retrospective, introducing potential confounding by indication that is challenging to fully resolve even with multivariable adjustment—CVC-treated patients in observational studies are systematically sicker at baseline, which can artifactually inflate CVC-associated mortality. Most studies have moderate sample sizes, limiting statistical power for mortality analyses. The definition of extravasation, monitoring protocols, PIV specifications, and outcome ascertainment methods differ substantially across studies, limiting precise pooled estimation. The only RCT (CENSER) was conducted at a single center in Thailand, limiting direct generalizability to diverse healthcare settings with different staffing models, CVC placement workflows, and patient populations.

Several areas require prioritization in future research. First, a multicenter, pragmatic randomized controlled trial directly comparing PIV versus CVC vasopressor initiation in ED septic shock patients—with standardized PIV protocols (gauge, site, concentration, monitoring) and pre-specified primary endpoints including 28-day mortality and extravasation rate—is the highest research priority. Such a trial is technically feasible given the widespread adoption of peripheral vasopressor protocols in contemporary practice. Second, prospective data on the optimal duration of peripheral vasopressor administration before transition to central access, and on the dose thresholds above which peripheral administration carries unacceptable extravasation risk, are urgently needed to inform protocol development. Third, economic analyses comparing the costs of CVC-associated complications (CLABSIs, mechanical injuries, prolonged ICU stays) against peripheral vasopressor monitoring requirements would clarify the health systems benefit of broader PIV vasopressor adoption. Finally, studies examining the impact of different peripheral access sites (antecubital, external jugular, midline catheter) and different vasopressor concentrations on extravasation risk would allow more precise protocol optimization.

The clinical implications of this systematic review are considerable. The accumulated evidence supports a paradigm shift in ED septic shock management: peripheral vasopressor initiation should be considered the standard initial approach in hemodynamically unstable septic shock patients who require immediate vasopressor therapy but who do not yet have central venous access. This approach should be accompanied by concurrent preparation for CVC placement, with transition to central access when therapy is expected to be prolonged (>4–6 hours), when peripheral access sites are inadequate, or when vasopressor doses exceed institutional protocol thresholds. ED physicians, emergency nurses, and critical care teams should be trained in peripheral vasopressor protocols including appropriate site selection (antecubital or proximal forearm, ≥18 gauge), concentration limits, monitoring frequency (minimum hourly site assessment), and the clinical signs prompting escalation of access strategy.

5. Conclusion

This systematic review of 10 verified, PubMed-indexed studies encompassing over 4,000 patients with septic shock demonstrates that peripheral vasopressor administration in the ED is safe, with extravasation rates of 0–4.5% in ED-specific studies, no documented severe tissue injury or limb ischemia, and no mortality disadvantage compared with central venous administration. PIV initiation is associated with faster vasopressor delivery (79–126 minutes earlier), reduced fluid resuscitation volumes, lower intubation rates, and CVC placement avoidance in approximately one-third of patients. The CENSER randomized trial provides the strongest evidence that early peripheral norepinephrine significantly improves shock control at 6 hours and reduces 28-day mortality compared with delayed standard care. These findings collectively support the incorporation of

peripheral vasopressor initiation protocols into ED septic shock management pathways, with concurrent planning for central venous access when prolonged or high-dose therapy is anticipated. A multicenter pragmatic RCT directly comparing PIV versus CVC vasopressor initiation with mortality as a primary endpoint remains the highest-priority research need in this field.

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