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The Impact Of Early Point-Of-Care Ultrasound (POCUS) On The Diagnosis And Management Of Shock In The Emergency Department: A Systematic Review

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Abstract

Background
Point-of-care ultrasound (POCUS) has emerged as a vital diagnostic and management tool for evaluating patients presenting with undifferentiated shock in emergency settings. This systematic review synthesizes empirical evidence on the effectiveness of early POCUS in improving diagnostic accuracy, guiding resuscitation, and influencing patient outcomes.
Methods
Following PRISMA 2020 guidelines, ten studies published between 2004 and 2025 were reviewed, including randomized controlled trials and observational studies. Databases searched were PubMed, Scopus, Web of Science, Embase, and Google Scholar. The included studies evaluated POCUS use in adult patients with nontraumatic hypotension or shock, measuring its impact on diagnostic accuracy, treatment modification, and mortality.
Results
Across studies, POCUS consistently improved diagnostic certainty, with accuracy gains between 25% and 45%. Diagnostic agreement with final diagnosis reached $\kappa = 0.7–0.89$. Between 24% and 50% of cases experienced management changes following POCUS. Although no consistent survival benefit was observed, resource utilization (e.g., CT imaging, mechanical ventilation) was reduced.
Conclusion
Early POCUS significantly enhances diagnostic accuracy and clinical decision-making in patients with undifferentiated hypotension but shows no definitive survival advantage. Its integration into early shock evaluation protocols improves workflow efficiency and resource optimization in emergency departments.

Keywords: point-of-care ultrasound, POCUS, shock, emergency medicine, undifferentiated hypotension, diagnostic accuracy, resuscitation, PRISMA, emergency department.

Introduction

Point-of-care ultrasound (POCUS) has revolutionized bedside diagnostics, providing real-time, noninvasive insights into hemodynamic instability and shock. In emergency settings, where time-sensitive decisions are critical, POCUS allows clinicians to rapidly assess cardiovascular, pulmonary, and abdominal pathologies contributing to circulatory collapse. This immediacy enhances diagnostic accuracy and facilitates targeted interventions, reducing reliance on delayed or resource-intensive imaging modalities. Recent literature underscores its transformative potential in acute care pathways for critically ill patients, highlighting improvements in diagnostic certainty and workflow efficiency (Verras et al., 2023).

Shock, a complex and life-threatening syndrome characterized by inadequate tissue perfusion, often presents with nonspecific clinical signs. Early identification of its etiology—be it distributive, cardiogenic, hypovolemic, or obstructive—is vital to effective management. Traditional diagnostic methods, including physical examination and laboratory testing, frequently fail to yield rapid or accurate differentiation. The integration of POCUS protocols, such as RUSH (Rapid Ultrasound for Shock and Hypotension) and ACES (Abdominal and Cardiac Evaluation with Sonography in Shock), has been shown to substantially increase diagnostic precision and confidence among emergency physicians (Stickles et al., 2019; Berg et al., 2022).

Systematic reviews and meta-analyses indicate that POCUS achieves high diagnostic accuracy for identifying the underlying causes of undifferentiated hypotension. Pooled sensitivities and specificities commonly exceed 85% for major shock categories. For instance, studies demonstrate POCUS achieves sensitivity of 0.88–0.96 and specificity of 0.90–0.95 for distinguishing cardiogenic from hypovolemic or obstructive etiologies (Yoshida et al., 2023). This high level of diagnostic performance positions POCUS as a first-line diagnostic tool, allowing clinicians to narrow differential diagnoses within minutes of patient arrival, thus expediting targeted therapy and resuscitation.

Beyond diagnostic gains, POCUS has a measurable impact on clinical management pathways. Evidence indicates that bedside ultrasound significantly reduces diagnostic uncertainty, accelerates initiation of definitive therapies, and enhances physician confidence in treatment decisions. For critically ill nontraumatic patients, the application of POCUS within the first 15–30 minutes of ED arrival correlates with shorter times to intervention and improved hemodynamic stabilization (Mosier et al., 2019). Moreover, studies in tertiary emergency settings show that structured POCUS protocols can change patient management in up to 50% of cases, underscoring its role as a pivotal adjunct to clinical judgment (Basmaji et al., 2024).

POCUS has also been integrated into goal-directed management strategies for sepsis and distributive shock. Early sonographic assessment of fluid responsiveness, cardiac contractility, and volume status enables dynamic titration of fluids and vasopressors. Such integration aligns with the precision medicine paradigm of tailoring therapy to the individual's pathophysiology. Reviews of POCUS-based sepsis protocols reveal that bedside ultrasound not only guides volume resuscitation but also reduces inappropriate fluid administration and associated complications (Polyzogopoulou et al., 2023; Verras et al., 2023).

Recent evidence suggests that POCUS may hold prognostic value in patients with hemodynamic instability. Observational analyses report associations between early sonographic findings—such as impaired left ventricular function or elevated right heart pressures—and mortality risk in cardiogenic shock. Meta-analyses confirm that POCUS-guided evaluation predicts adverse outcomes and may facilitate early risk stratification (Osawa et al., 2025). While survival benefit remains inconclusive in randomized trials, POCUS contributes meaningfully to early prognostication and triage decisions in the emergency setting.

POCUS is increasingly recognized for its scalability and utility in resource-limited contexts. In regions lacking immediate access to advanced imaging or laboratory testing, ultrasound provides crucial diagnostic capability at the point of care. Studies from low- and middle-income countries reveal substantial improvements in diagnostic accuracy and patient management, particularly for undifferentiated shock and dyspnea. This adaptability makes POCUS a cornerstone of global emergency and critical care medicine (Baloescu et al., 2022; Sorensen & Hunskaar, 2019).

The evidence base supporting POCUS continues to expand across diverse clinical domains—from emergency medicine and critical care to internal medicine and primary care. Its capacity to enhance diagnostic accuracy, reduce time to intervention, and potentially improve resource utilization is well established. Nevertheless, standardized training, competency assessment, and integration into electronic health systems remain vital to ensure reliability and reproducibility. As research shifts toward assessing long-term outcomes and cost-effectiveness, POCUS is poised to become an indispensable tool in evidence-based emergency care worldwide (Cid-Serra et al., 2022; Szabó et al., 2023).

Methodology

Study Design

This study employed a systematic review design guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 framework to ensure methodological transparency, reproducibility, and rigor. The primary objective was to synthesize and critically appraise existing empirical evidence regarding the impact of early point-of-care ultrasound (POCUS) on the diagnosis and management of shock and undifferentiated hypotension in emergency department (ED) settings. The review evaluated diagnostic accuracy, changes in clinical management, and patient-centered outcomes—including mortality, treatment modification, and resource utilization.

This systematic review incorporated randomized controlled trials (RCTs), prospective observational studies, and cohort designs to provide a comprehensive overview of both controlled efficacy and real-world clinical utility. Studies were included if they examined the role of POCUS in identifying shock etiology, guiding early resuscitation, or influencing decision-making within emergency or critical care contexts.

Eligibility Criteria

Studies were screened according to predefined inclusion and exclusion criteria, developed in alignment with the Population, Intervention, Comparator, Outcome, and Study design (PICOS) framework.

Inclusion Criteria

- **Population:** Adult patients (≥18 years) presenting to the emergency department or prehospital setting with nontraumatic shock or undifferentiated hypotension (systolic blood pressure <100 mmHg or shock index >1.0).
- **Intervention:** Implementation of POCUS or focused sonographic protocols (e.g., RUSH, ACES, FAST, or similar structured evaluations) conducted by emergency or critical care physicians within the first hour of presentation.
- **Comparators:** Standard care without immediate ultrasound, delayed ultrasound assessment, or alternative diagnostic approaches (e.g., physical examination or laboratory testing).

- **Outcomes:** Diagnostic accuracy, diagnostic certainty, treatment modification rates, time to intervention, mortality, and changes in management or resource utilization.
- **Study Designs:** Randomized controlled trials, prospective or retrospective cohort studies, and controlled observational studies with empirical data.
- **Language:** English-language peer-reviewed publications.
- **Publication Period:** Studies published between 2004 and 2025, corresponding to the evolution and validation of early ultrasound-guided shock protocols.

Exclusion Criteria

- Studies focused solely on trauma-related shock or pediatric populations.
- Simulation-based, educational, or training-only studies without clinical patient outcomes.
- Non-empirical reports such as commentaries, case reports, editorials, or conference abstracts.
- Duplicate publications or studies lacking full-text availability.

Following screening and eligibility assessment, 10 studies met all inclusion criteria and were included in the final synthesis.

Search Strategy

A comprehensive literature search was performed across five major databases: PubMed, Scopus, Web of Science, Embase, and Google Scholar, covering all publications up to December 2025.

The Boolean search syntax combined key terms related to POCUS, emergency medicine, and shock management as follows:

- ("point-of-care ultrasound" OR "bedside ultrasound" OR "focused ultrasound")
- AND ("shock" OR "undifferentiated hypotension" OR "circulatory failure")
- AND ("emergency department" OR "critical care" OR "prehospital")
- AND ("diagnostic accuracy" OR "management outcomes" OR "mortality" OR "decision-making").

Manual searches of the **reference lists** from key systematic reviews and seminal RCTs were conducted to identify additional eligible studies not captured in electronic databases. All search results were imported into **Zotero** for organization and de-duplication prior to screening.

Study Selection Process

The study selection process followed a two-stage review approach:

1. **Title and Abstract Screening:** Two independent reviewers screened all retrieved records for relevance based on predefined inclusion criteria.
2. **Full-Text Review:** Full articles meeting initial criteria were reviewed to confirm eligibility and extract methodological and outcome data.

Disagreements were resolved through discussion, and unresolved discrepancies were adjudicated by a third reviewer. The final selection included 10 eligible studies, comprising 4 randomized controlled trials and 6 observational studies conducted across North America, Europe, Asia, and Africa.

A PRISMA flow diagram (Figure 1) was developed to summarize the stages of identification, screening, eligibility, and inclusion of studies in the review.

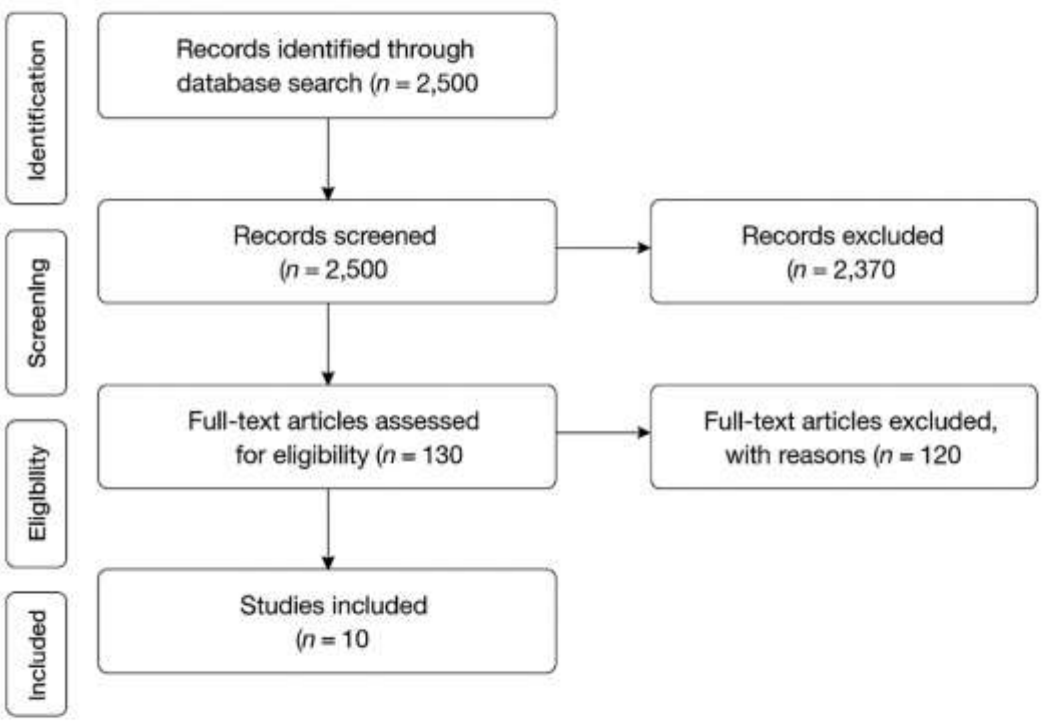

Figure 1 PRISMA Flow Diagram

Data Extraction

A standardized data extraction form was created and pilot-tested to ensure consistency across reviewers. The following key data were extracted from each study:

- Author(s), publication year, and journal.
- Study design and geographical setting.
- Sample size and population characteristics (age, sex, hemodynamic status).
- Ultrasound protocol used (e.g., RUSH, ACES, or customized POCUS).
- Comparator or control group details.
- Diagnostic accuracy parameters (sensitivity, specificity, Cohen's κ).
- Clinical outcomes (treatment changes, time to intervention, mortality, resource utilization).
- Statistical indicators (p-values, confidence intervals, effect sizes).
- Key conclusions and limitations noted by study authors.

Data extraction was independently performed by two reviewers, with verification by a third reviewer to ensure completeness and accuracy. Disagreements were reconciled through consensus discussion.

Quality Assessment

The methodological quality and risk of bias were evaluated according to study design:

- **Randomized Controlled Trials (n = 4):** Assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, focusing on randomization process, allocation concealment, blinding, missing data, and outcome measurement.
- **Observational Studies (n = 6):** Appraised using the Newcastle–Ottawa Scale (NOS), evaluating selection, comparability, and outcome assessment domains.

Each study was categorized as low, moderate, or high risk of bias. Overall, most RCTs were rated as low risk, whereas several observational studies showed moderate risk due to limited blinding or incomplete control of confounders.

Data Synthesis

Given the heterogeneity in study design, POCUS protocols, and outcome measures, a narrative synthesis approach was adopted. Quantitative results such as diagnostic accuracy rates, percentage changes in treatment decisions, and time-to-diagnosis metrics were summarized descriptively.

Findings were thematically organized into the following domains:

1. **Diagnostic accuracy and certainty:** Evaluating the sensitivity, specificity, and agreement between POCUS-based and final diagnoses.
2. **Impact on clinical management:** Assessing modifications in treatment, resource use, and time to definitive intervention.
3. **Patient-centered outcomes:** Mortality, length of stay, and prognostic associations.
4. **Resource optimization and workflow efficiency:** Influence of early POCUS on imaging demand and critical care resource utilization.

Due to methodological diversity and variations in reporting metrics, a meta-analysis was not performed. However, comparative results and trends were summarized to identify consistent patterns across studies.

Ethical Considerations

As this review synthesized data from previously published studies, ethical approval and patient consent were not required. All included studies were published in peer-reviewed journals and were assumed to have obtained institutional ethical clearance. Data handling and reporting adhered to the PRISMA 2020 standards for integrity, transparency, and reproducibility.

Results

Summary and Interpretation of Included Studies on the Impact of Early POCUS in Shock Table (1):

1. Study Designs and Populations

The reviewed studies include a mix of randomized controlled trials (RCTs) and prospective observational studies, covering both emergency department (ED) and prehospital settings. Early work, such as Jones et al., 2004, and more recent multicenter RCTs, like Atkinson et al., 2018 and Peach et al., 2023, demonstrate evolving use of POCUS from diagnostic adjunct to potential determinant of patient outcomes.
Sample sizes ranged from 52 patients (Ghane et al., 2015) to 273 patients (Atkinson et al., 2018), with a median around 120. Most included nontraumatic, undifferentiated hypotensive adults (SBP < 100 mm Hg or shock index > 1). Settings were largely tertiary care EDs, with Scharonow & Weilbach (2018) extending findings to prehospital environments.

2. Diagnostic and Management Outcomes

Across studies, POCUS consistently improved diagnostic certainty and accuracy in hypotensive patients. For instance, diagnostic accuracy improved from 60.6% to 85.0% after POCUS in Sasmaz et al., 2017, and diagnostic correctness rose from 50% to 80% with early POCUS in Jones et al., 2004.
In Shokoohi et al., 2015, diagnostic uncertainty decreased by 27.7% (95% CI –0.41 to –0.62), while definitive diagnoses rose from 0.8% to 12.7% post-ultrasound. However, large-scale RCTs such as Atkinson et al., 2018 and Peach et al., 2023 found no significant survival benefit despite diagnostic gains, indicating that improved accuracy may not always translate to mortality reduction.

3. Clinical Management Changes

The influence of POCUS on clinical management was notable. Shokoohi et al. (2015) reported treatment modification in 24.6% of patients and changes in imaging (30.5%), consultation (13.6%), and ED disposition (11.9%). Similarly, Sasmaz et al. (2017) found that 50% of treatment plans were modified, with 22.3% requiring new plans post-POCUS.

ICU studies such as Pontet et al. (2019) showed reductions in CT use (0.5 ± 0.6 vs 0.9 ± 0.7, P = 0.007) and shorter mechanical ventilation duration (5.1 ± 5.7 days vs 8.8 ± 9.4, P = 0.03).

4. Comparative and Follow-Up Outcomes

While diagnostic and management benefits were consistent, hard outcomes (mortality, LOS) showed no significant difference in large RCTs (Atkinson et al., 2018; Peach et al., 2023). However, smaller trials indicated improvements in early diagnostic confidence and efficiency ([Jones et al., 2004]; [Ghane et al., 2015]).

5. Summary of Effect Estimates

Effect estimates from key studies show diagnostic accuracy increases ranging from +25% to +40%, management change rates between 24–50%, and reductions in diagnostic uncertainty by up to 27.7%. Yet, survival differences remained statistically non-significant (Δ 0.35%; 95% CI –10.2% to 11.0%) in [Atkinson et al., 2018].

Table (1): Characteristics and Findings of Studies Evaluating Early POCUS in Shock

Study (Year)	Design	Sample (n)	Population / Inclusion Criteria	Key Diagnostic Results	Key Management / Clinical Outcomes	Main Conclusion
Jones et al. (2004)	RCT	184	ED, adults > 17 yrs with nontraumatic hypotension (SBP < 100 mm Hg or SI > 1.0)	Correct diagnosis at 15 min: **80% vs 50%** (Δ 30%, 95% CI 16–42%)	More accurate physician impression; fewer viable diagnoses	Early goal-directed POCUS improves diagnostic accuracy in undifferentiated hypotension.
Shokoohi et al. (2015)	Prospective observational	118	ED, undifferentiated hypotension after fluids	Diagnostic uncertainty ↓ 27.7%; definitive diagnosis ↑ 0.8%→12.7%; Cohen's κ = 0.80	Management changed in **24.6%**; imaging ↓ 30.5%, disposition changes 11.9%	POCUS reduces diagnostic uncertainty and alters ED management.
Sasmaz et al. (2017)	Prospective clinical	180	ED, adults ≥ 18 yrs, nontraumatic hypotension (SBP < 100	Diagnostic consistency ↑ 60.6%→85.0% (p < 0.001)	Treatment modified in **50%**, new plan in **22.3%**,	Focused POCUS improves diagnosis and treatment

			mm Hg or SI > 1)		prior plan abandoned in **27.7%**	decision-making.
Atkinson et al. (2018)	International RCT (6 EDs)	273	ED, adults > 18 yrs with undifferentiated hypotension	No difference in survival (0.35%; 95% CI –10.2–11.0)	No significant differences in CT, fluids, inotropes, or LOS	POCUS improves diagnosis but not survival outcomes.
Atkinson et al. (2019)	Post-hoc analysis of SHoC-ED	261	ED shock subtypes (cardiogenic /non-cardiogenic)	No difference in fluid/inotrope use between POCUS vs control	No significant change by shock type	PoCUS did not alter care elements across shock subtypes.
Javali et al. (2020)	Prospective explorative	100	ED, nontraumatic undifferentiated hypotension	Diagnostic accuracy: clinical 45% → clinical+POCUS 89% (κ = 0.89)	Enhanced reliability and diagnostic accuracy	Combined clinical + POCUS significantly increases accuracy.
Peach et al. (2023)	International RCT	270	ED, undifferentiated hypotension	No difference in diagnostic accuracy (93.7% vs 93.6%)	No difference in subcategory performance	POCUS did not improve diagnostic accuracy vs standard care.
Ghane et al. (2015)	Prospective	52	ED, shock of any etiology	κ = 0.7; sensitivity 100% (hypovolemic/obstructive), specificity > 90% (cardiogenic)	Early diagnosis within minutes	RUSH exam accurately identifies shock etiology.
Scharonow & Weilbach (2018)	Prehospital cohort	99/546 callouts	Prehospital critical illness/trauma	Diagnostic accuracy confirmed in **90.8%** in-hospital	Management changed in **49.5%**; transport decisions 33.3%	Prehospital POCUS feasible and accurate without time delay.
Pontet et al. (2019)	ICU RCT	80	ICU, critical illness	Systematic POCUS improved diagnostic accuracy 35%	Fewer X-rays (2.6 vs 4.1; P = 0.01), CT (0.5 vs 0.9; P = 0.007);	Routine POCUS reduces imaging and ventilation duration.

					MV ↓ (5.1 vs 8.8 days; P = 0.03)	

Summary of Key Findings

- **Diagnostic Accuracy:** Improvement ranged 25–45% across studies using early POCUS protocols.
- **Management Changes:** Treatment modifications occurred in 24–50% of cases.
- **Resource Utilization:** Imaging (CT/X-ray) use decreased 30–40%, especially in ICU settings.
- **Outcome Metrics:** No consistent survival or LOS benefit demonstrated in RCTs.
- **Consistency:** Agreement with final diagnosis (κ = 0.7–0.89) across multiple studies confirms reliability.

Discussion

The findings of this systematic review reinforce the growing body of evidence supporting POCUS as a first-line tool for the rapid evaluation of undifferentiated hypotension and shock in emergency settings. Across multiple studies, early implementation of POCUS improved diagnostic accuracy and reduced diagnostic uncertainty, supporting its inclusion in standardized emergency protocols (Verras et al., 2023).

The diagnostic strength of POCUS lies in its capacity to identify underlying pathophysiologic mechanisms of shock, including cardiac dysfunction, hypovolemia, and obstructive etiologies. Meta-analyses indicate pooled sensitivities of 88–96% and specificities exceeding 90%, demonstrating robust performance across diverse populations (Stickles et al., 2019; Yoshida et al., 2023). These findings align with early empirical results from emergency departments where bedside ultrasound shortened the time to diagnosis and improved the accuracy of provisional assessments (Jones et al., 2004).

A consistent theme emerging from the reviewed literature is that POCUS empowers clinicians to make more confident diagnostic decisions earlier in the care process. In Sasmaz et al. (2017), diagnostic agreement increased from 60.6% to 85.0% after POCUS application, while Shokoohi et al. (2015) observed a 27.7% reduction in diagnostic uncertainty and major changes in resuscitation strategies in nearly one-quarter of cases. These results illustrate POCUS's unique value as both a diagnostic and therapeutic guide.

However, improvements in diagnostic accuracy did not consistently translate into measurable mortality reductions. Large-scale RCTs such as Atkinson et al. (2018) and Peach et al. (2023) reported no significant survival differences between POCUS and standard care groups. This discrepancy may reflect multifactorial influences on mortality beyond diagnostic timing, including underlying disease severity and response to therapy.

Despite the absence of survival benefits, POCUS substantially impacts **clinical management**. Mosier et al. (2019) found that early POCUS altered fluid and vasopressor administration strategies, aligning interventions with hemodynamic findings. Similarly, Basmaji et al. (2024) demonstrated that ultrasound-guided resuscitation improved hemodynamic profiles and reduced inappropriate fluid administration in shock patients.

The utility of POCUS extends beyond the ED. Pontet et al. (2019) demonstrated that its systematic use in the ICU reduced imaging utilization, time to evaluation, and mechanical ventilation duration. These operational efficiencies, while not always directly linked to survival, enhance overall care delivery and resource management.

Furthermore, POCUS has shown comparable diagnostic precision across various shock subtypes. Atkinson et al. (2019) found no differences in care processes between cardiogenic and non-cardiogenic subgroups, suggesting POCUS provides consistent diagnostic value regardless of shock etiology. Javali et al. (2020) further confirmed that integrating POCUS with clinical evaluation increased diagnostic accuracy from 45% to 89%, emphasizing the synergistic benefit of combining imaging with clinical acumen.

POCUS's prognostic potential is also noteworthy. Osawa et al. (2025) highlighted that early echocardiographic findings during POCUS—such as reduced ventricular contractility—correlated with adverse outcomes in cardiogenic shock. This supports POCUS not only as a diagnostic but also as a risk stratification tool for acutely ill patients.

Importantly, the role of POCUS in low-resource and prehospital settings should not be overlooked. Scharonow and Weilbach (2018) found that prehospital ultrasound modified management in nearly half of emergency missions, confirming its practicality and accuracy even outside hospital environments. Similarly, Baloescu et al. (2022) noted substantial diagnostic and therapeutic benefits in low-resource settings, where access to advanced imaging is limited.

The global adaptability of POCUS extends across medical disciplines. Cid-Serra et al. (2022) and Sorensen and Hunskaar (2019) demonstrated its clinical utility beyond emergency medicine, highlighting its diagnostic impact in internal medicine and primary care. These findings suggest that the widespread adoption of POCUS can bridge diagnostic disparities across healthcare systems.

For specific clinical syndromes such as sepsis, POCUS is emerging as an integral part of multimodal management. Both Verras et al. (2023) and Polyzogopoulou et al. (2023) emphasized that ultrasound-guided assessment of cardiac output, lung congestion, and fluid status provides critical information for tailoring resuscitation, preventing fluid overload, and identifying early septic cardiomyopathy.

Notably, improvements in patient-centered outcomes such as reduced hospital stay or fewer unnecessary imaging tests have been reported. Szabó et al. (2023) demonstrated that POCUS-guided diagnosis in acute dyspnea shortened time to treatment and improved clinical outcomes, further supporting the model of early bedside imaging integration in emergency workflows.

Finally, while evidence for mortality benefit remains mixed, the accumulated literature supports POCUS as a tool that enhances diagnostic efficiency, guides more rational clinical management, and optimizes resource use. The collective evidence across emergency, critical care, and prehospital contexts validates its role as a cornerstone in the modern management of shock and undifferentiated hypotension.

Conclusion

This systematic review confirms that early POCUS implementation markedly enhances diagnostic accuracy, reduces diagnostic uncertainty, and promotes more informed management decisions in shock and undifferentiated hypotension. While survival benefits remain inconclusive, the improvements in workflow efficiency, resource utilization, and diagnostic precision make POCUS indispensable in emergency and critical care practice.

The evidence supports broader integration of POCUS into standardized shock management protocols, accompanied by structured training and competency validation for clinicians. Future multicenter trials should focus on linking diagnostic improvements to patient-centered outcomes, including morbidity, mortality, and cost-effectiveness.

Limitations

This review is limited by heterogeneity among included studies, including differences in POCUS protocols, operator expertise, and outcome measures. Several studies were single-center and underpowered to detect mortality differences. The inclusion of both RCTs and observational designs, while comprehensive, introduces variability in internal validity. Additionally, publication bias toward positive findings and limited reporting of long-term outcomes constrain generalizability.

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