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Critical care pharmacists in intensive care units: A meta-analysis of their impact on mortality and adverse drug events

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Abstract

Introduction: Critical care pharmacists (CCPs) are increasingly integrated into intensive care unit (ICU) teams to enhance medication safety and improve outcomes. However, their effect on mortality and adverse drug events (ADEs) remains inadequately studied.

Objective: This study aimed to evaluate the impact of CCP involvement in ICU care on patient mortality and ADEs.

Methods: A comprehensive systematic review and meta-analysis were performed, encompassing studies published through January 2025. The literature search was conducted in multiple databases, such as PubMed, Embase, and the Cochrane Library.

Results: A total of 16 eligible studies were identified, collectively involving 37,925 ICU patients. To evaluate outcomes, odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated utilizing either fixed-effects or random-effects models, depending on heterogeneity levels. Patients in ICUs with CCPs experienced significantly reduced mortality (OR: 0.72; 95% CI: 0.56 – 0.92; p=0.01) and fewer ADEs (OR: 0.39; 95% CI: 0.21 – 0.70; p=0.002) compared to controls. Despite notable heterogeneity, findings were consistent in sensitivity analyses. No significant publication bias was detected.

Conclusion: The inclusion of CCPs in ICU teams is associated with lower mortality and fewer ADEs. These findings support expanding the role of pharmacists in critical care settings.

Keywords: Critical care pharmacists; Pharmacotherapy; Intensive care unit; Adverse drug events; Mortality; Interdisciplinary care

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1. Introduction

In the evolving landscape of critical care, intensivist-led multidisciplinary teams have become a cornerstone of best practices in the intensive care unit (ICU).[1] These teams are designed to deliver timely, accurate, and collaborative care to critically ill patients, thereby

improving patient recovery and minimizing excessive consumption of healthcare resources. Among the essential, yet sometimes underappreciated, members of these teams are critical care pharmacists (CCPs).[2] Their integration into ICU care has increasingly been recognized as an indispensable strategy to enhance therapeutic outcomes and reduce medication-related risks.[3-5] Moreover, the evolving landscape of intensive care presents increasingly complex pharmacotherapeutic challenges, driven by the rapid development of new drugs, emerging antimicrobial resistance patterns, and high rates of comorbidities among ICU patients.[6-8] CCPs are uniquely positioned to address these dynamics by ensuring the implementation of up-to-date medication practices, assessing evolving pharmacokinetics in critically ill patients, and managing drug-related toxicities.[9,10] Their expertise in emergency drug resuscitation protocols and knowledge of high-alert medications further reinforces their critical contribution to ICU safety.[11]

CCPs possess specialized training and clinical expertise in pharmacotherapy, particularly in high-acuity settings. Their roles transcend traditional pharmacy duties, encompassing real-time decision-making, participation in multidisciplinary rounds, individualization of medication regimens, dose adjustments based on organ function, management of drug interactions, and oversight of medication safety protocols.[12,13] This allows for a more proactive approach to patient care in the ICU, where complex drug regimens and rapid physiological changes demand constant monitoring and adjustment.[2]

Evidence suggests that the involvement of CCPs leads to a higher implementation rate of pharmacotherapeutic recommendations.[14] These interventions include dosage adjustments, therapeutic drug monitoring, and the prevention or resolution of adverse drug events (ADEs). In addition, CCPs serve as valuable resources in formulating and adhering to institutional guidelines, conducting staff education, and contributing to antimicrobial stewardship initiatives, all of which are vital in managing critically ill patients, particularly those with sepsis, multi-organ failure, or polypharmacy.[15,16]

A growing body of literature supports the contribution of CCPs to improved patient outcomes in the ICU. Previous studies have shown that their participation reduces preventable ADEs, medication errors, and overall hospital costs. For example, a frequently referenced meta-analysis conducted by Wang *et al.*[14] reported a significant decrease in ADEs following pharmacist-led interventions. However, the study did not find a definitive impact on the incidence of medication errors. It is worth noting that the patient populations analyzed were not limited to the ICU; instead, they largely encompassed individuals from general medical and surgical wards. This broader scope limits the direct relevance of the findings to critically ill populations, where clinical dynamics and pharmacotherapeutic challenges differ substantially.

Furthermore, the aforementioned meta-analysis[14] faced limitations related to small sample sizes, study heterogeneity, and a high risk of bias, which called into question the strength and generalizability of its conclusions. In addition, these earlier evaluations lacked a focus on mortality outcomes and did not disaggregate results by clinical setting. As a result, the true impact of CCPs in the ICU remains inadequately quantified, particularly with regard to patient survival and the incidence of medication-related problems (MRPs).

Beyond reducing ADEs, CCPs are also believed to contribute indirectly to lowering ICU mortality rates.[3,17,18] Their recommendations often lead to more appropriate and timely initiation of therapies such as antibiotics, vasopressors, or anticoagulants, which are critical in managing life-threatening conditions. For example, inappropriate antimicrobial therapy has been linked to increased mortality in sepsis patients; thus, pharmacist-led antimicrobial stewardship can be life-saving.[15] Moreover, by assuming responsibilities related to medication safety and efficacy, CCPs allow intensivists and nurses to focus more on other aspects of patient care, potentially reducing the risk of oversight and burnout among ICU staff.[2,19]

Despite these potential benefits, the extent of CCPs' influence on clinical outcomes such as ADEs and mortality has not been thoroughly evaluated in a comprehensive, ICU-specific meta-analysis. Previous studies have either lacked adequate statistical power, failed to isolate the ICU as a unique clinical environment, or focused only on surrogate outcomes like cost savings or error rates rather than clinically significant endpoints.

This knowledge gap underscores the need for more rigorous evaluation. To date, no meta-analysis has been exclusively dedicated to assessing the influence of CCPs on both mortality and ADEs in ICU populations. Therefore, the current study aims to address this gap by conducting a comprehensive meta-analysis focused specifically on the inclusion of CCPs in ICU teams and their impact on these two critical outcomes.

The objective of this meta-analysis is to systematically assess and quantify the impact of CCPs on clinical outcomes among ICU patients, with a primary focus on mortality and ADEs. In addition to these primary endpoints, the study also explores secondary outcomes where data are available, including ICU length of stay,

ventilator days, cost-related implications, and the broader clinical roles of CCPs such as antimicrobial stewardship, pharmacotherapy optimization, and interdisciplinary care contributions. This comprehensive approach aims to inform evidence-based policy and practice regarding the integration of pharmacists into critical care teams.

2. Methods

2.1. Study design

This investigation was designed as a systematic review and meta-analysis, adhering to both the Meta-analysis of Observational Studies in Epidemiology framework and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[20] Its primary aim was to consolidate and evaluate existing evidence on the clinical impact of integrating CCPs within ICU teams, specifically focusing on two key outcomes: patient mortality and the incidence of ADEs. The study is registered in the International Prospective Register of Systematic Reviews under the number CRD420251080799.

2.2. Eligibility criteria

Study selection was guided by clearly defined inclusion and exclusion criteria established in advance to maintain methodological integrity and ensure the relevance of the included research.

Inclusion criteria were as follows:

(i) The analysis encompassed a range of study designs, including randomized controlled trials, prospective cohort studies, and retrospective observational investigations.
(ii) The patient population consisted exclusively of individuals admitted to ICUs.
(iii) The intervention involved the integration or presence of CCPs as active members of the ICU care team.
(iv) The study reported clinical outcomes, specifically mortality and/or ADEs, comparing an intervention group (with CCPs) against a control group (without CCP involvement).

Exclusion criteria were as follows:

(i) Studies that did not explicitly evaluate the impact of CCPs on either mortality or ADEs.
(ii) Studies where the intervention involved pharmacy services not specific to critical care or not clearly involving pharmacists embedded in ICU teams.
(iii) Publications lacking a comparison group, such as single-arm studies, editorials, review articles, conference abstracts, commentaries, or letters to the editor.

2.3. Literature search strategy

The search strategy was based on the PICOS framework: P (Population): ICU patients; I (Intervention): involvement of CCPs; C (Comparison): care without CCPs; O (Outcomes): mortality and ADEs; S (Study Design): randomized controlled trials, prospective cohort studies, and retrospective observational studies.[21] A comprehensive and systematic literature search was performed across three major electronic databases: PubMed, Embase, and the Cochrane Library. The search spanned from database inception through January 2025. Keywords and Medical Subject Headings included "intensive care unit," "critical care pharmacists," "adverse drug events," "death," and "multidisciplinary." The specific search strategies for each database are detailed in Table 1. Boolean operators (AND and OR) were employed to ensure a sensitive and inclusive search.

Duplicate entries were removed using EndNote software, after which two reviewers independently screened the remaining titles and abstracts. Full-text versions of studies deemed potentially eligible were retrieved and evaluated for inclusion according to the predefined criteria.

2.4. Data collection and quality evaluation

Data were systematically collected using a standardized and pre-tested data extraction form. From each eligible study, the following key information was obtained:

(i) First author and publication year
(ii) Country and healthcare setting
(iii) Study design and duration
(iv) Number of participants in the intervention and control groups
(v) Patient characteristics
(vi) Nature of the pharmacist intervention
(vii) Clinical outcomes (mortality and ADEs)
(viii) Reported effect sizes and confidence intervals (CIs).

Table 1. Structured search strategies used across selected databases

Database	Search strategy
PubMed	#1 "critical care pharmacists" (MeSH Terms) OR "intensive care unit" (MeSH Terms) OR "adverse drug events" (All Fields) #2 "multi-disciplinary" (MeSH Terms) OR "death" (All Fields) #3 #1 AND #2
Embase	"critical care pharmacists"/exp OR "intensive care unit"/exp OR "adverse drug events"/exp #2 "multidisciplinary"/exp OR "death"/exp #3 #1 AND #2
Cochrane Library	#1 (critical care pharmacists): ti, ab, kw OR (intensive care unit): ti, ab, kw OR (adverse drug events): ti, ab, kw (Word variations have been searched) #2 (multidisciplinary): ti, ab, kw OR (death): ti, ab, kw (Word variations have been searched) #3 #1 AND #2

Abbreviation: MeSH: Medical Subject Headings.

Methodological quality was evaluated using the Cochrane Risk of Bias Tool for randomized controlled trials, and an adapted version of the Newcastle-Ottawa Scale was employed for observational studies. Risk of bias assessments were independently performed by two reviewers to ensure objectivity and consistency.[22] Any disagreements were resolved through consensus between the reviewers, and, when necessary, a third reviewer was consulted to reach a final decision.

Bias levels were rated as low, moderate, or high, based on how adequately studies addressed core methodological elements, including participant selection, intervention implementation, outcome measurement, attrition handling, and reporting transparency.

2.5. Statistical analysis

The meta-analysis was performed using Review Manager version 5.3, provided by the Nordic Cochrane Centre. For binary outcomes such as mortality and ADEs, odds ratios (ORs) with corresponding 95% CIs were calculated using either fixed-effects or random-effects models, depending on the degree of heterogeneity among the included studies.

Heterogeneity was quantified using the I^2 statistic, interpreted as follows:[23]

- I^2 value of 0% indicates no observed heterogeneity
- I^2 value of 25% reflects low heterogeneity
- I^2 value of 50% suggests a moderate level of heterogeneity
- I^2 value of 75% or higher represents substantial or high heterogeneity.

When the I^2 statistic exceeded 50%, indicating moderate to high heterogeneity, a random-effects model was employed to account for inter-study variability. For lower levels of heterogeneity, a fixed-effects model was applied. Where data permitted, subgroup analyses were planned to investigate potential sources of variability across studies.

To evaluate the robustness of the results, sensitivity analyses were performed by excluding studies deemed to have a high risk of bias or those with small sample sizes ($n \leq 100$). Potential publication bias was assessed visually through funnel plot inspection and statistically using Egger's regression test.[24] A p=0.05 or higher was interpreted as no significant publication bias.

2.6. Outcome measures

The primary outcomes assessed were:

(i) Mortality: Defined as all-cause in-hospital or ICU death, as reported in each study.

(ii) ADEs: Defined as any harm associated with medication use, including medication errors, adverse drug reactions, or other preventable injuries, according to the criteria specified in each individual study.

All outcomes were reported as aggregate effect sizes, and subgroup comparisons were performed where data were available.

3. Results

3.1. Study selection and characteristics

Out of a total of 3,301 unique records identified through the comprehensive database search, 16 studies met the predefined eligibility criteria and were included in the final meta-analysis (Figure 1).[25-40] These studies were published between 1999 and 2022 and collectively enrolled 37,925 patients admitted to ICUs. Of these, 23,060 patients received care involving CCPs, while 14,865 patients served as controls (i.e., managed without the involvement of CCPs).

The included studies varied in design, comprising both prospective and retrospective observational cohorts, as well as interventional trials, and were conducted across multiple countries, including the United States, China, Belgium, Thailand, Egypt, and India. Sample sizes of individual studies ranged widely, from as few as 70 patients to as many as 30,032 (Table 2). The interventions performed by CCPs included direct participation in ICU rounds, antimicrobial stewardship, pain and sedation management, prevention of drug interactions, and optimization of pharmacotherapy in critical illness.

3.2. Impact on mortality

A pooled analysis of all 16 studies demonstrated a significant reduction in mortality associated with the inclusion of CCPs in ICU teams. The overall OR for mortality was 0.72, with a 95% CI of 0.56 – 0.92 (p=0.01), favoring the intervention group (Figure 2). Patients receiving care with CCP involvement had a 28% lower likelihood of mortality compared to those managed without pharmacist involvement.

Nonetheless, the analysis demonstrated substantial heterogeneity across the included studies, as reflected by an I^2 statistic of 78% (Figure 2). This considerable variation in effect sizes is likely attributable to differences in study methodologies, patient populations, and the nature of pharmacist-led interventions. As a result, the use of a random-effects model was deemed appropriate to account for this variability.

3.3. Impact on ADEs

The meta-analysis also revealed a substantial reduction in the incidence of ADEs among patients managed with CCP

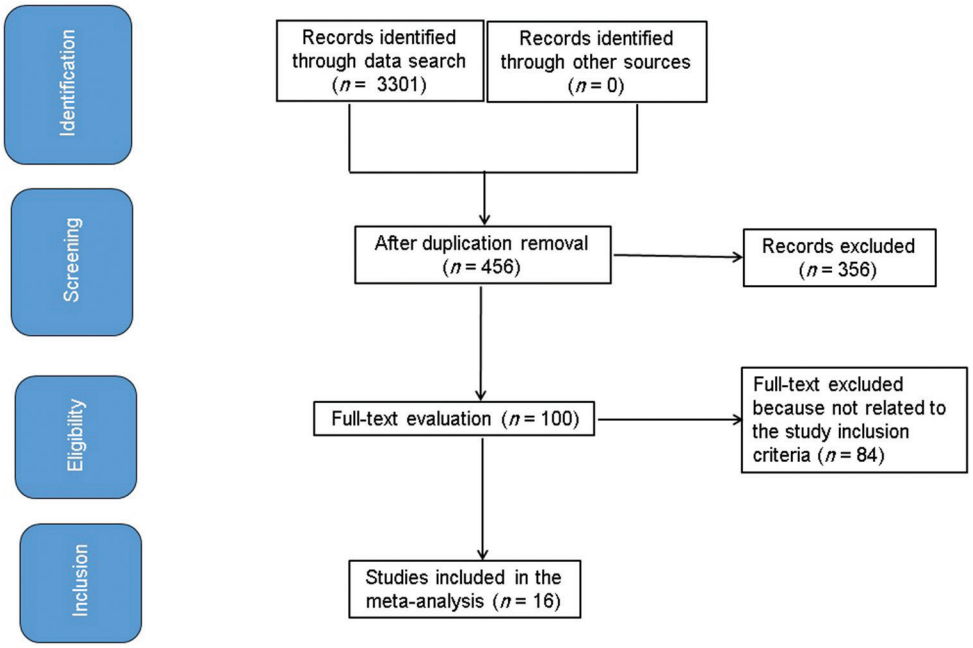

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram illustrating the study selection process for the meta-analysis

Table 2. Summary of key characteristics of studies included in the meta-analysis

Study	Country	Total	Critical care pharmacist	Control
Leape *et al.*[25]	USA	150	75	75
MacLaren *et al.*[37]	USA	30,023	18,804	11,219
Rivkin and Yin[26]	USA	266	137	129
Jiang *et al.*[27]	China	144	73	71
Jiang, *et al.*[38]	China	180	93	87
Jiang, *et al.*[28]	China	209	106	103
Claus *et al.*[29]	Belgium	155	80	75
Oxman *et al.*[30]	USA	92	42	50
Hammond *et al.*[31]	USA	219	118	101
Li *et al.*[32]	China	577	353	224
Dilokpattanamongkol *et al.*[39]	Thailand	156	66	90
Louzon *et al.*[33]	USA	70	35	35
Gu *et al.*[34]	China	2,872	1,436	1,436
Aghili and Kasturirangan[35]	India	228	211	17
Toukhy *et al.*[36]	Egypt	2,480	1,379	1,101
Mohammad *et al.* [40]	USA	104	52	52
Total		37,925	23,060	14,865

Abbreviation: USA: United States of America.

involvement. The pooled OR for ADEs was 0.39 (95% CI: 0.21 – 0.70, p=0.002), indicating a 61% reduction in the odds of experiencing an ADE when CCPs were integrated into the ICU care team (Figure 3).

As with mortality, the analysis of ADE outcomes showed significant heterogeneity (I^2 = 83%), prompting the use of a random-effects model to account for inter-study differences. Despite this heterogeneity, the association remained statistically robust, supporting the positive role of CCPs in minimizing MRPs in critical care settings.

3.4. Publication bias and funnel plot analysis

To assess the risk of publication bias, funnel plots were constructed for both mortality and ADE outcomes (Figures 4 and 5). The plots appeared symmetric, and Egger's regression test yielded a p=0.87, suggesting no significant publication bias for either outcome.

3.5. Sensitivity analysis

Sensitivity analyses were conducted to evaluate the stability of the results. Excluding studies with small sample sizes ($n \leq 100$) and those with a high risk of bias did not materially alter the overall findings, thereby reinforcing the reliability of the conclusions.

3.6. Subgroup observations

Although data limitations prevented formal subgroup analyses by age, gender, or ethnicity, a narrative synthesis of selected studies highlighted consistent benefits of CCP inclusion across different regions and ICU types (e.g., medical, surgical, and trauma). Furthermore, studies incorporating CCPs with well-defined clinical roles, such as daily patient rounds and antimicrobial stewardship,

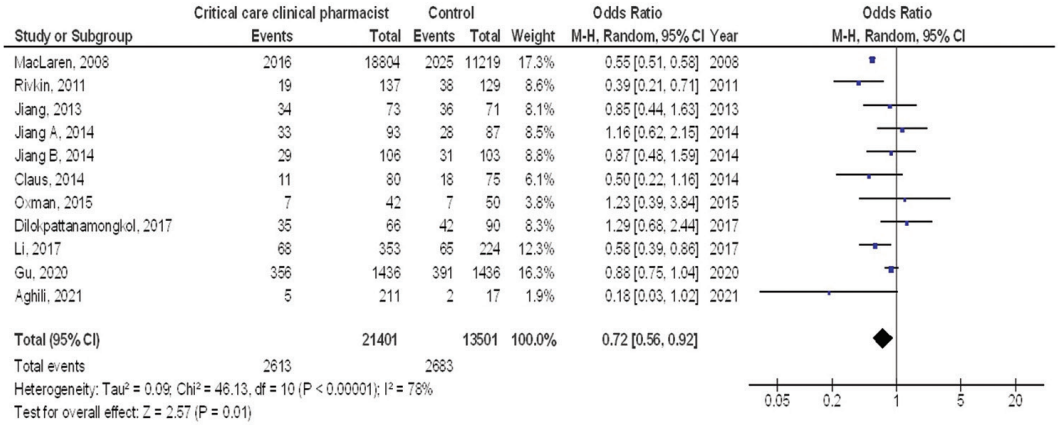

Figure 2. Forest plot comparing intensive care unit mortality rates between patients managed with and without critical care pharmacist involvement

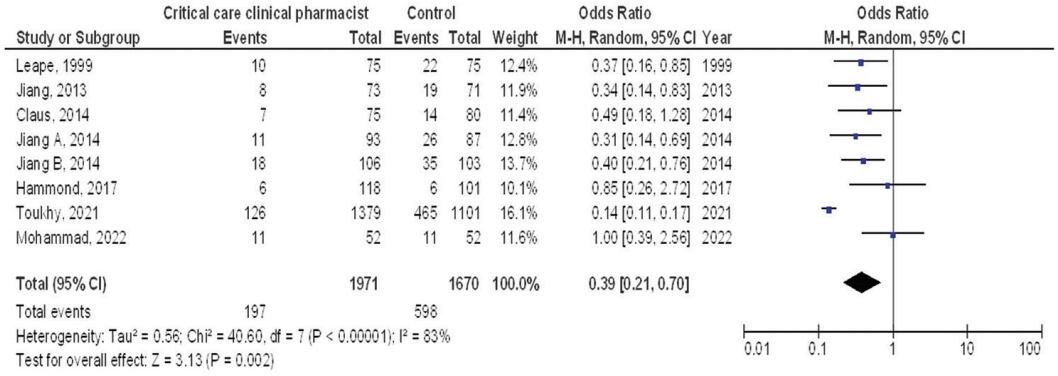

Figure 3. Forest plot illustrating the effect of critical care pharmacist involvement on the rate of adverse drug events among intensive care unit patients, compared to standard care without pharmacist participation

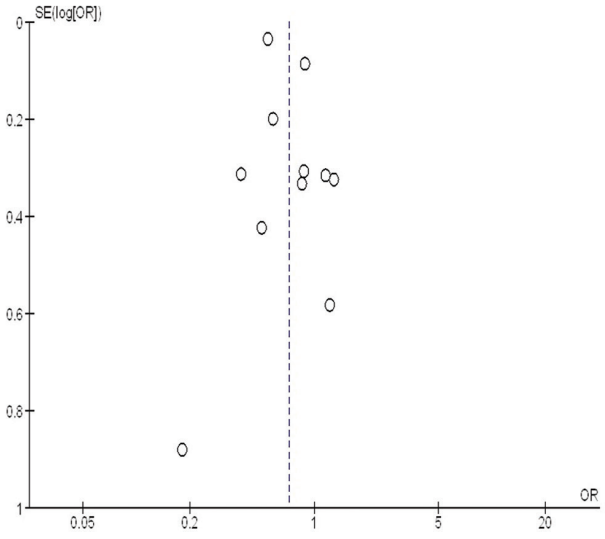

Figure 4. Funnel plot evaluating potential publication bias in mortality outcomes
Abbreviations: OR: Odds ratio; SE: Standard error

reported more pronounced improvements in mortality and ADEs.

3.7. Summary of study characteristics

Detailed characteristics of the included studies are presented in Table 2. Most studies were conducted in tertiary academic centers, and the interventions typically involved CCPs making direct pharmacotherapeutic recommendations during interdisciplinary rounds. Several studies also documented CCP contributions to institutional policy development, formulary management, and healthcare staff education, all of which may have contributed to improved outcomes.

4. Discussion

This meta-analysis, involving 16 studies and 37,925 ICU patients, presents strong evidence that integrating CCPs into ICUs is significantly associated with reduced mortality and a lower incidence of ADEs. The findings

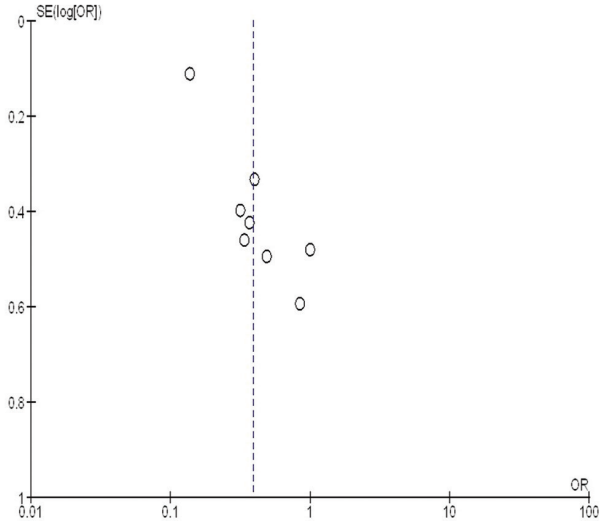

Figure 5. Funnel plot examining potential publication bias associated with adverse drug event outcomes
Abbreviations: Or: Odds ratio; SE: Standard error

support previous literature and underscore the clinical and operational value of pharmacist-led interventions in high-acuity environments. Clinicians in the ICU face difficult-to-manage situations and complex patients daily, and without appropriate pharmacological oversight, these challenges can lead to fatal complications.[41] CCPs with particular experiences can help decrease complex MRPs when integrated into ICU teams.[42]

The inclusion of CCPs may also decrease the workload of other ICU staff by redistributing responsibilities.[41] Reduced workloads have been associated with lower ICU mortality by minimizing medical errors and improving access to critical equipment.[43] By contributing to an interdisciplinary team, CCPs can play a vital role in reducing mortality, which is a key indicator of ICU care quality.[44] Moreover, ADEs are often fatal in critically ill patients,[45] reinforcing the importance of medication safety interventions.

The 28% reduction in mortality observed in ICUs with CCP involvement is particularly noteworthy. Mortality in critical care is influenced by multiple intersecting variables, including disease severity, timeliness and appropriateness of treatment, comorbidities, and care coordination. Pharmacists help optimize several of these factors, especially through the identification and prevention of drug-related problems, timely therapeutic adjustments, and reduction of iatrogenesis harm. The mortality benefit observed in this analysis likely reflects CCPs' proactive role in early pharmacotherapy optimization in the clinical trajectory, which is essential in conditions such as sepsis, acute respiratory distress syndrome, or multi-organ failure.

This study revealed that ICU team care involving CCPs decreased the occurrence of ADEs. The incidence of ADEs is influenced by the clinical setting and the nature of interventions. ADEs contribute significantly to healthcare costs, particularly through insurance claims; therefore, reducing their occurrence represents a major advantage for ICU patients.[46] The observed 61% reduction in ADEs supports the role of CCPs in improving medication safety. In the ICU, ADEs are frequently linked to polypharmacy, organ dysfunction, drug–drug interactions (DDIs), and medications with narrow therapeutic indices. CCPs bring specialized expertise to address these challenges, ensuring appropriate dosing and monitoring of medications. Their interventions range from preventing nephrotoxic drug combinations to adjusting antibiotic regimens based on pharmacokinetic parameters, actions that directly mitigate the risk of ADEs.

These findings align with earlier meta-analyses. For example, Wang *et al.*[14] demonstrated that CCP interventions were effective in reducing ADEs in general hospital settings. However, their analysis did not show a significant effect on mortality and did not focus specifically on ICU populations. Our results not only reaffirm the benefit of CCPs in reducing ADEs but also extend prior research by demonstrating a clear mortality advantage specific to ICU settings, which represent the most complex and high-risk environment for medication management.

In a more recent systematic review, Lee *et al.*[3] highlighted improvements in ICU outcomes when pharmacists participated in multidisciplinary care. However, their analysis did not quantify ADEs, and the mortality data were more limited. Our work thus provides a more comprehensive synthesis of both safety and survival endpoints and fills an important evidence gap in the literature on ICU pharmacotherapy.

The study by Rivkin and Yin[26] demonstrated that CCPs significantly reduce clinically important DDIs in medical ICU patients. Prospective pharmacist review during rounds led to a 65% reduction in severe DDIs requiring therapy modification or avoidance (classified as categories D and X; $p<0.01$), with an 82% acceptance rate of pharmacist recommendations. Notably, fewer DDIs were associated with shorter ICU length of stay ($p<0.01$), though the direct impact on mortality was not statistically significant ($p=0.09$). The intervention group had a lower mortality rate (13.9% vs. 29.5%, $p=0.01$), suggesting broader benefits of pharmacist involvement beyond DDI management. This highlights the pharmacist's role in mitigating MRPs and optimizing ICU outcomes through proactive, team-based interventions.

Aghili and Kasturirangan[35] investigated the role of clinical pharmacists in managing DDIs among

critically ill patients with chronic kidney disease (CKD), demonstrating their significant impact on medication safety. The study identified 273 DDIs in 76 patients (83.5% of participants), with 63.7% requiring close monitoring and 30% necessitating therapy modification or drug discontinuation. Pharmacist interventions, including dosage adjustments (19.4%), drug discontinuation (17.2%), and enhanced monitoring (41%), were highly accepted by prescribers (92%). Notably, 22% of DDIs caused temporary harm or prolonged hospitalization, but pharmacist involvement mitigated severe outcomes, such as life-threatening hypotension from contraindicated combinations (e.g., nitroglycerine-sildenafil). The study also highlighted that advanced CKD stages (e.g., stage 5) and polypharmacy significantly increased DDI risk ($p<0.05$). These findings underscore the critical role of pharmacists in preventing ADEs through proactive DDI management, particularly in high-risk CKD populations, though their impact on mortality remains unexplored.

Dilokpattanamongkol *et al.*[39] evaluated the impact of pharmacist-led pharmaceutical care on pain and agitation management in a Thai medical ICU, demonstrating significant improvements in clinical outcomes. The study found that pharmacist involvement in analgesic/sedative selection reduced median ICU length of stay (from 10.00 to 6.50 days, $p=0.002$), hospital stay (from 30.50 to 17.50 days, $p<0.001$), and ventilator days (from 14.00 to 8.50 days, $p=0.008$). Pharmacists optimized therapy by promoting opioid-based regimens over benzodiazepines, which decreased adverse events like prolonged sedation (from 24.44% to 4.55%, $p=0.001$) and hemodynamic instability (from 18.89% to 3.03%, $p=0.003$). However, mortality rates remained unchanged (53.03% vs. 46.67%, $p=0.432$), likely due to the multifactorial nature of ICU mortality. The study highlights the role of CCPs in protocol-driven sedation management to enhance recovery and resource utilization, though their impact on survival may require broader multidisciplinary interventions.

The study by Louzon *et al.*[33] demonstrated the significant impact of CCPs in managing pain, agitation, and delirium through multidisciplinary ABCDE bundle rounds. Their two-phase initiative showed that pharmacist-directed sedation management reduced continuous sedation exposure by 46%, decreased ICU length of stay by 5 days, and lowered hospital costs by $1.2 million. In addition, the expanded ABCDE bundle program further improved outcomes, including a reduction in mean ventilator days from 5.6 to 4.0 days and a significant decline in mortality Acute Physiology and Chronic Health Evaluation ratios from 1.26 to 0.75. These findings underscore the role of pharmacists in optimizing clinical outcomes and reducing resource utilization in ICUs, aligning with broader evidence supporting their integration into critical care teams.

Mohammad *et al.*[40] evaluated the role of clinical pharmacists in an interprofessional ICU recovery clinic, demonstrating their effectiveness in addressing MRPs among ICU survivors. The study found that pharmacist interventions led to a significant reduction in MRPs between initial and six-month follow-up visits (from 3.5 ± 1.7 to 2.4 ± 1.3 per patient, $p=0.025$), with common interventions including patient education (91.3%), medication changes (73.9%), and care coordination (73.9%). Although no significant difference in MRPs was observed between the intervention and control groups, the high acceptance of pharmacist recommendations (e.g., addressing safety-related issues, drug interactions, and adherence) underscores their value in post-ICU care. The authors emphasized the pharmacist's role in comprehensive medication management, particularly for complex sepsis or respiratory failure survivors, highlighting potential long-term benefits in reducing preventable readmissions and optimizing recovery. These findings align with broader evidence supporting pharmacist integration in critical care transitions to mitigate ADEs and improve patient outcomes.

The study by Oxman *et al.*[30] evaluated the impact of pharmacist-driven interventions on antibiotic de-escalation in suspected ventilator-associated pneumonia cases. Pharmacist involvement significantly improved the rate of appropriate antibiotic targeting based on culture results (59% pre-intervention vs. 91% post-intervention, $p=0.003$), demonstrating their role in optimizing antimicrobial stewardship. However, the intervention did not significantly increase early antibiotic discontinuation in low-risk patients (19% vs. 23%, $p=0.767$), suggesting physician reluctance to stop empiric therapy despite clinical indicators. While mortality rates remained unchanged (14% vs. 16.7%, $p=0.72$), the study highlights the pharmacist's ability to enhance evidence-based antibiotic use in critical care, particularly in tailoring therapy to microbiological data.

The study by Jiang *et al.*[28] highlights the role of CCPs in optimizing antimicrobial dosing for patients undergoing continuous venovenous hemofiltration (CVVH), demonstrating significant reductions in ADEs and cost savings. Pharmacist interventions, including daily dosing adjustments based on dynamic CVVH parameters, led to a 2.36-fold decrease in antimicrobial-related ADEs (11 vs. 26 events, $p=0.002$) and cost savings of £1637.7 per patient. Notably, β-lactams accounted for 51.2% of dosing errors, underscoring the complexity of antimicrobial management in renal replacement therapy. While mortality and ICU length of stay remained unchanged, the study emphasizes

the pharmacist's impact on preventing preventable ADEs (4 vs. 14 events, p=0.006) and reducing drug costs, reinforcing their value in multidisciplinary ICU teams.

The study by Hammond *et al.*[31] evaluated the impact of pharmacist-led educational interventions on the appropriateness of stress ulcer prophylaxis (SUP) in critically ill patients. The intervention, which included guideline-based education and pocket cards for physicians, significantly reduced inappropriate initiation of acid suppression therapy (AST) from 23% to 11% (p=0.012). While no differences were observed in mortality or adverse events (e.g., pneumonia, *Clostridium difficile* infection), the study demonstrated that pharmacist involvement in education improved adherence to evidence-based SUP practices. This highlights the role of CCPs in optimizing medication safety and reducing unnecessary therapy, though broader interventions may be needed to address inappropriate continuation of AST beyond the ICU.

In a study performed by Pronovost *et al.*,[1] apposite pharmacist recommendations for antibiotic treatment in critically ill patients were associated with a decline in ventilator-related pneumonia, which is often linked to higher mortality. Furthermore, a study by Kim *et al.*[47] showed that, compared to patients who did not receive team-based care with CCP, mortality was lower among those managed by an ICU team that incorporated CCPs.

An earlier meta-analysis focusing on the influence of ICU CCPs' interventions on medication errors and ADEs showed a decrease in ADEs when a CCP was added to the team.[14] However, the data were derived from subjects admitted to general medical or surgical units rather than ICU settings, and the definition of medication errors was unclear.

A previous study by Leape *et al.*[25] demonstrated the significant impact of integrating pharmacists into ICU rounds, showing a 66% reduction in preventable ADEs, from 10.4 to 3.5/1,000 patient-days, after implementing pharmacist participation. The study, conducted in a medical ICU, highlighted that nearly all (99%) of the pharmacists' recommendations were accepted by physicians, with interventions ranging from dose corrections to identifying drug interactions and allergies. The authors estimated annual cost savings of approximately $270,000 due to prevented ADEs, underscoring the pharmacist's role in error prevention, interception, and systems improvement. These findings support the value of pharmacists as active members of the ICU team in enhancing medication safety and reducing harm.

Several mechanisms likely explain the observed outcomes:

(i) Medication error prevention: CCPs review and reconcile medications daily, preventing errors in dosing, duplications, and omissions, especially during care transitions.
(ii) Therapeutic optimization: Pharmacists tailor treatments based on patient-specific variables, including renal/hepatic function, weight, drug levels, and drug interactions.
(iii) Antimicrobial stewardship: Several studies (e.g., Jiang *et al.*[27,28,38] and Li *et al.*[32]) in this meta-analysis demonstrated that CCP-led antimicrobial programs reduced inappropriate antibiotic use and potentially minimized resistance patterns, leading to improved infection-related outcomes.
(iv) Education and protocol development: CCPs contribute to policy and protocol development and offer bedside education, increasing adherence to evidence-based guidelines.
(v) Interdisciplinary synergy: Pharmacists free up physician time by managing medication-related tasks, contributing to more efficient workflows and reducing clinician burnout, a factor indirectly tied to fewer clinical errors.

A notable strength of this meta-analysis is its inclusion of studies from diverse regions, such as North America, Asia, Europe, and Africa. This diversity supports the global applicability of the findings. Even in middle-income countries, such as Egypt and India, where resource constraints may be more prominent, CCPs demonstrated measurable improvements in patient safety and outcomes. This suggests that pharmacist integration is not only a high-income health system luxury but also a universally impactful intervention when appropriately implemented.

In resource-limited settings, CCPs may have even greater importance, given the scarcity of intensivists, suboptimal nurse-to-patient ratios, and high patient turnover. The pharmacist's vigilance and expertise can serve as a vital safety net in such environments.

This study demonstrated a significant association between the inclusion of CCPs in ICU teams and reductions in both mortality and ADEs. However, further high-quality trials are needed to clarify the specific clinical contexts and mechanisms through which these benefits occur. In addition, our meta-analysis did not identify any significant associations between outcomes and patient characteristics such as age, ethnicity, or gender. This finding is consistent with previous meta-analyses, which also reported no clear influence of these demographic factors on the observed outcomes.[3,48]

Incorporating CCPs should be considered a standard component of ICU staffing models, especially given

the magnitude of benefit demonstrated. Policymakers and healthcare leaders should advocate for expanding pharmacist roles in the ICU beyond the traditional scope. Furthermore, educational and professional development programs must be tailored to produce pharmacists with the advanced competencies required for critical care practice. This integration may also be cost-effective. Although our analysis did not focus on economic outcomes, prior studies have shown that pharmacist interventions lead to reduced length of stay, MRPs, and lower hospital readmissions, all contributing to healthcare cost savings.[48,49]

5. Limitations

Despite the compelling results, several limitations should be acknowledged:

(i) Heterogeneity: There was significant heterogeneity among the included studies in terms of design, sample size, CCP roles, and outcome definitions. While random-effects modeling mitigates this statistically, clinical heterogeneity remains a consideration.

(ii) Study design: Only a few of the included studies were randomized trials; most were observational, potentially introducing bias.

(iii) Inadequate subgroup data: The inability to perform subgroup analyses based on variables such as age, gender, severity scores, ICU type (e.g., medical vs. surgical), and comorbidities limits the granularity of the findings.

(iv) Lack of long-term outcomes: Most studies reported only in-hospital outcomes. The long-term impact of CCPs on quality of life, post-ICU syndrome, or 90-day mortality remains to be clarified.

(v) Economic evaluation: While improved clinical outcomes often translate to cost savings, this analysis did not explore cost-effectiveness, which is an essential consideration for implementation.

6. Conclusion

This systematic review and meta-analysis provide compelling evidence that the incorporation of CCPs into ICU teams is associated with significantly lower mortality and fewer ADEs among critically ill patients. The findings reinforce the importance of pharmacist-led pharmacotherapy optimization, antimicrobial stewardship, and interdisciplinary collaboration in intensive care settings. Given the clinical relevance of these outcomes and the increasing complexity of ICU pharmacotherapy, healthcare institutions and policymakers should consider the routine deployment of CCPs as a strategic priority. Future studies should aim to address remaining gaps, including the cost-effectiveness of CCP services, long-term patient outcomes, and their impact across various ICU subtypes and demographic groups. Ultimately, integrating CCPs represents not only a pharmacological intervention but also a structural advancement in ICU team-based care, contributing to safer, more efficient, and outcome-driven patient management.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

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Ethics approval and consent to participate

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Availability of data

The data analyzed in this meta-analysis were extracted from publicly available publications, with full citations and article links provided in the references section.

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