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Impact of pharmacists during in-hospital resuscitation or medical emergency response events: A systematic review

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ABSTRACT

Background: We sought to determine the impact of the presence of a pharmacist on medication and patient related outcomes during the emergency management of critically ill patients requiring resuscitation or medical emergency response team care in a hospital setting.
Methods: We conducted a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A literature search of databases from January 1995 to April 2023 was conducted to identify studies of contemporary pharmacist practice. Results were extracted and analysed for included studies, those evaluating the impact of the presence of a pharmacist on medication and patient related outcomes during the emergency management of critically ill hospitalised patients requiring resuscitation or medical emergency response team care. To determine risk of bias, the Newcastle-Ottowa Quality Assessment scale was used for non-randomised studies and the Revised Cochrane risk-of-bias tool for randomised trials.
Results: Of 1345 studies identified, 54 were selected for full text review, and 30 were included in the final analysis. There were 29 cohort studies and one randomised controlled trial. The studies reported the impact of a pharmacist for a variety of patient presentations. The study team assigned each study to one of eight patient cohorts: acute stroke, cardiac arrest, rapid response calls, S-T segment elevation myocardial infarction, acute haemorrhage, major trauma resuscitation, sepsis and status epilepticus. The most frequently reported outcome, associated with a statistically significant benefit in 23 studies, was time to medication administration. Few studies reported a significant difference in patient outcome measures such as mortality. Only 8 of the 30 studies were assessed to have a low risk of bias.
Conclusions: The results of this systematic review provide support for a beneficial impact of a pharmacist presence and intervention during resuscitation or medical emergency response team care, with significant improvements in outcomes such as time to initiation of time-critical medications, medication appropriateness and guideline compliance. However, studies were predominantly small and retrospective and were not powered to detect differences in patient related measures such as length of stay and mortality. Future research should investigate the clinical impacts of the pharmacist in ED resuscitation settings in controlled, prospective studies with robust sampling methods.

1. Introduction

Medication safety in the acute care setting represents a significant challenge [1]. It has been estimated that medication errors occur in 5% of all drug administrations [2] and preventable adverse drug events occur in 1.6% of hospitalised patients [3]. Medication errors are common in emergency departments (ED). A study of 192 patients in a United States (US) ED found that 59.4% of ED patients had one or more medication error and 37% had one or more medication errors that were not intercepted before administration [4].

The reasons for medication errors are multifactorial. Emergency clinicians work in overcrowded, time-pressured environments in which the risk of medication error is high [5-9]. Overcrowding in EDs has been recognised as a widespread problem in many countries [10-13] and has been shown to increase the risk of medication errors and delays in the administration of time critical medications [10,14-16].

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In the ED, the use of verbal medication orders is common and multitasking is needed to manage workload. These strategies have been associated with an increased risk of prescribing and administration errors and can lead to patient harm [5-7]. Within this hazardous environment, emergency physicians and nurses often need to quickly prescribe and administer high-risk or time-critical medications to critically ill patients, with errors involving high-risk medications are more likely to result in significant patient harm [17,18].

In-hospital, medical emergencies and resuscitation events also occur outside of the ED. High-risk medications are used by medical emergency teams to manage patients and the potential for medication error in this setting is extremely high [19,20]. Similar to the ED resuscitation setting, in-hospital medical emergencies, are fast-paced, requiring quick decision making, use of verbal orders and rapid administration of medications [20]. A prospective, observational evaluation of 50 medical emergency responses found that one out of two doses of medications given during these events were administered with an error [20]. The results of studies of pharmacists participating in medical emergency or rapid response teams are relevant to an investigation of pharmacists' impact on medication and patient related outcomes when working as part of ED resuscitation teams because the patient acuity managed, medications used and clinician time pressures are similar. We included studies in inpatient resuscitation and medical emergency response settings as part of this investigation to ascertain if there are studies with demonstrable pharmacist-led impacts on outcomes which may provide learning for EM pharmacy practice in the ED resuscitation setting.

Involvement in resuscitation has been identified as an emerging area of practice for EM pharmacists and is currently considered standard of care by pharmacy practice standards in the US [21-24]. A 2016 US survey revealed that 98% of EM pharmacists participated in resuscitation responses, commonly performing “emergency response” activities which were defined as responding to medical emergencies such as cardiopulmonary arrest, trauma resuscitation, myocardial infarction and stroke [25]. In Canada surveys reveal that between 61 and 77% of pharmacist respondents perform trauma or resuscitation care [26,27]. In Australia in 2016, 9 out of 35 hospitals (27%) had EM pharmacists directly involved in the care of patients requiring resuscitation [21]. The role of the pharmacist during in-hospital resuscitation or medical emergency response teams has also been described [28-30]. A large population study found that hospitals with clinical pharmacist participation on the cardiopulmonary resuscitation team had associated reduced overall mortality rates [31]. However, the effectiveness and benefits of pharmacists on medication and patient related outcomes while practicing within a medical emergency or ED resuscitation team have not been fully identified or described.

The objective of this systematic review was to identify and critically appraise studies evaluating the impact of the presence of a pharmacist on medication and patient related outcomes during the emergency management of critically ill patients requiring resuscitation or medical emergency response team care in a hospital setting.

2. Methods

2.1. Study design and search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology was used. A protocol was registered with the International Prospective Register of Systematic Reviews prior to study initiation (PROSPERO2021 CRD42021285683 https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021285683).

A search of the following databases was conducted from 1 January 1995 to 8 September 2022 and updated on 15 April 2023; PubMed, Embase, International Pharmaceutical Abstracts, The Cumulative Index to Nursing and Allied Health Literature (CINAHL), Scopus, and Cochrane Database of Systematic Reviews. We hand searched references of included studies and relevant review articles. A grey literature search of Google Scholar was performed on 8 September 2022. The search strategy was designed by the principal investigator (EC) with input from an experienced librarian and members of the research team (NF and MB). It included terms related to pharmacists and the management of acute critical events. We limited the database search from 1995 onwards to reflect contemporary clinical pharmacy practice and standards of modern healthcare systems.

2.2. Eligibility criteria

English language, peer reviewed, primary studies of patients requiring resuscitation or emergency management of an acute critical illness in a hospital setting were eligible. We excluded abstract-only studies, case reports, narrative or systematic reviews, and guidelines. We used a patients-intervention-comparison-outcomes format to determine the eligibility of studies for inclusion:

- Patient population: Studies of critically ill patients requiring resuscitation or medical emergency response team care in hospital
- Intervention: Pharmacist impact as part of a resuscitation or medical emergency response team, on patient or medication related outcomes
- Comparison: Concurrent or historical controls who received resuscitation or medical emergency response team care when a pharmacist was not present
- Outcomes: (1) Patient related: length of stay (LOS) in hospital, intensive care unit (ICU) or ED, hospital readmission, mortality, discharge disposition; (2) Process outcomes: adherence to evidence-based practice or guidelines; (3) Medication related outcomes: time from ED arrival to medication administration, appropriateness of medication, medication error, medication harm; (4) Reported cost savings due to reduced drug costs

Medication error was defined as “any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer” [32].

2.3. Study selection

All identified studies were imported into Covidence® systematic review software [33]. Two investigators (EC and NF) independently performed a title and abstract review to assess relevance and select studies for full text review. Any conflicts were resolved by a consensus discussion involving a third reviewer [34].

2.4. Data collection and processing

Publications selected for full text review were independently assessed for inclusion by two members of the research team (EC and NF or MB). A checklist was developed with input from the research team to identify data items, key outcomes and to identify patient cohorts. All outcome results were collected. Data was extracted from the included studies by EC and confirmed by a second reviewer (NF or MB). Discrepancies were resolved by discussion within the team. Data from the reviewed studies were entered into a predesigned Microsoft Excel® spreadsheet created by EC. The following study characteristics were collected: country of origin, study setting, study design, patient population and level of evidence as per the Australian National Health and Medical Research Council classification system [35]. Each study was assigned to one of 8 patient cohorts to cohesively describe the

range of patient presentations, group similar studies, and summarise in a table.

2.5. Risk of bias and quality assessment

To determine risk of bias (RoB) the Newcastle-Ottowa Quality Assessment scale (NOS) [36] was used for non-randomised studies and the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2) [37]. In addition, five Quality Assessment criteria that weren't addressed by the NOS tool were used to describe the presence or absence of robust study methods, as performed in the systematic review by Roman et al. [22] Specifically, the criteria assessed whether the study methodology included double data extraction, explicit record review, blinded assessmentand power calculation. Retrospective cohort studies were also assessed for the presence of a statistical adjustment approach to address potential confounding. The formal quality assessment of all included studies was conducted independently by two reviewers and any disagreement was resolved by consensus during research team discussions.

3. Results

3.1. Study selection

After removal of duplicates, 1500 studies were identified. Following abstract and title screening, 54 studies were identified for full text review. Of these, 30 studies met the inclusion criteria and were included in the review. Fig. 1 depicts the PRISMA flow diagram.

3.2. Study characteristics and patient populations

The characteristics of each study including study setting, duration and design, level of evidence, patient cohort, population and intervention and control group descriptions from the 30 included studies are summarised in Table 1. Of these, 29 were retrospective cohort studies, [28,39-65] including eight before and after study designs [43,45,46,50,54,62,63]. All but three studies, set in Japan and Australia [51,63], were conducted in the US. There were 25 studies set in the ED [28,39-41,43,45,47-49,52-59,61-67] and five studies

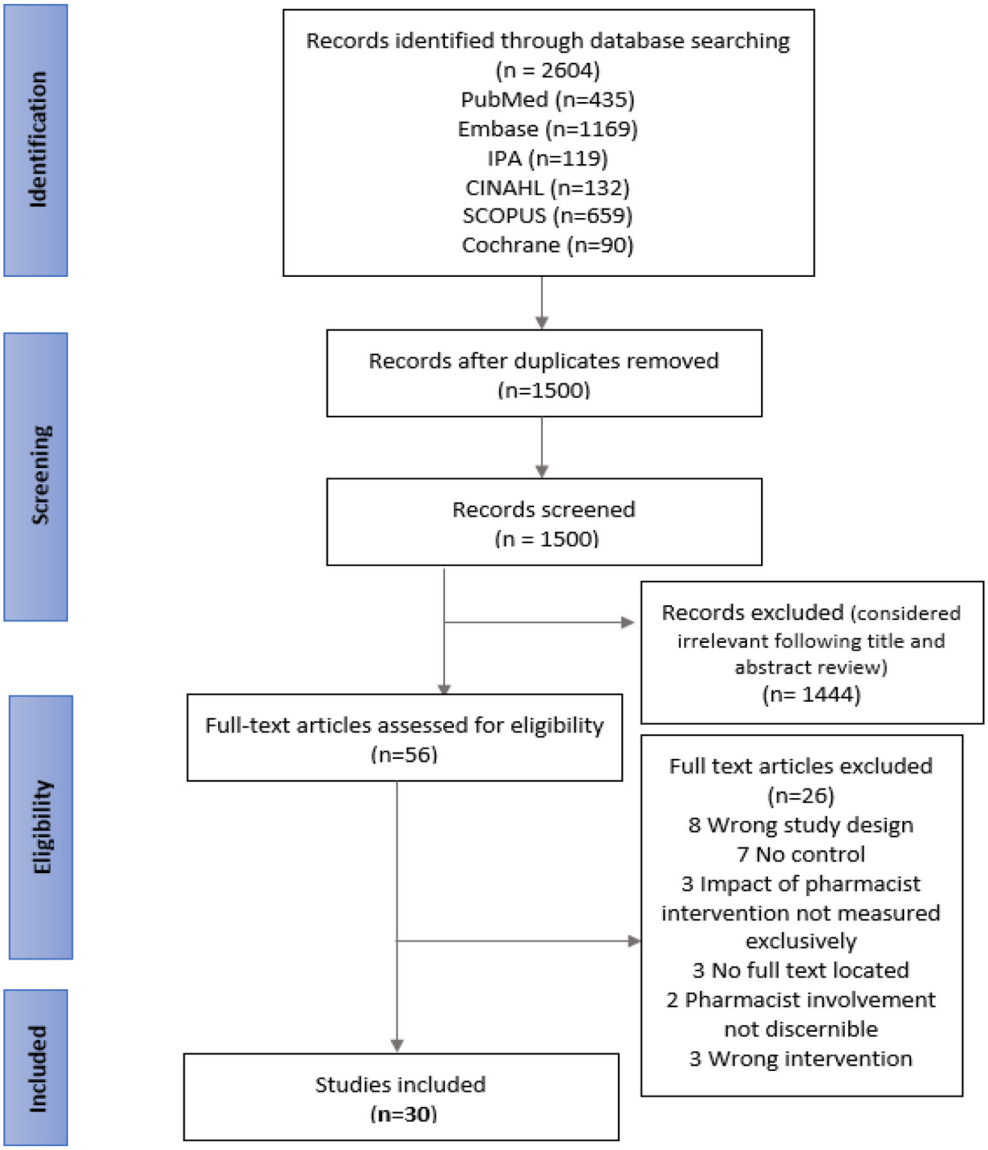

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses [38] flow diagram.

Table 1
Summary of study characteristics, study design with rating of level of evidence[a], and description of study populations (n) outcomes, results and statistical significance

Author, Year Published	Country/Setting Study duration	Study design (level of evidence)[a]	Patient population (*n*)	Intervention group (*n*)	Control group (*n*)
Barbour 2022 [45]	US / ED August 2016–May 2020	Cohort study III-2	Adults presenting to the ED who received IV alteplase for AIS ($n = 164$)	Pharmacist present at the bedside during acute stroke management ($n = 31$)	Pharmacist not present (outside stroke alert hours) ($n = 133$)
Gilbert 2019 [53]	US / ED Nov 2017–May 2018, May–Oct 2017	Historical Control study III-3	Adults who received rTPA for AIS in the ED ($n = 65$)	Pharmacist present during acute stroke management ($n = 33$)	Pharmacist not present (historical control) ($n = 32$)
Gosser 2016 [52]	US / ED Jan 2008–Oct 2012	Cohort study III-2	Adults who received IV rTPA for AIS in the ED ($n = 105$)	Pharmacist present during acute stroke management ($n = 67$)	Pharmacist not present during stroke alert ($n = 38$)
Jacoby 2018 [56]	US / ED Aug 2012–Aug 201	Cohort study III-2	Adults who received rTPA for AIS in the ED ($n = 100$)	Pharmacist present during acute stroke management ($n = 49$)	Pharmacist not present during response ($n = 51$)
McSwain 2022 [68]	US / ED Jan 2014–Dec 2018	Cohort study III-2	Adults who received IV alteplase for AIS ($n = 159$)	Pharmacist present during acute stroke management ($n = 40$)	Pharmacist not present during stroke team activation ($n = 119$)
Montgomery 2016 [63]	US / ED Jan 2012–Sept 2014	Cohort study III-2	Adults presenting to ED who received thrombolytics ($n = 97$)	Pharmacist present during acute stroke management ($n = 38$)	Pharmacist absent during stroke alert response ($n = 59$)
Rech 2017 [64]	US / ED and inpatients Jan 2012–Dec 2015	Cohort study III-2	Adults with acute ischemic stroke in ED or as an inpatient who received alteplase ($n = 125$)	Stroke competent pharmacist present during acute stroke management ($n = 45$)	Pharmacist not present ($n = 80$)
Roman 2021 [67]	Aus / ED Dec 2011 to Jun 2014, Jul 2014–Dec 2019	Historical control study III-3	Adults with AIS who received thrombolysis in ED within pharmacist working hours ($n = 186$)	Post implementation of addition of a pharmacist to the acute stroke team ($n = 122$)	Pre-implementation of addition of pharmacist to the acute stroke team ($n = 64$)
Draper 2008 [48]	US / inpatients Jan 2003–Jun 2004	Cohort study III-2	Adults with cardiopulmonary arrest while an inpatient ($n = 74$)	Presence of pharmacist on the CPR team ($n = 27$)	Pharmacist not present during CPR ($n = 47$)
Heavner 2017 [54]	US / inpatients Jan 2012–Dec 2013	Historical control study III-3	All cardiac arrest events ($n = 80$)	Integrated pharmacist on the cardiac arrest team ($n = 54$)	Pre-implementation of pharmacist on cardiac arrest team ($n = 26$)
McAllister 2017 [61]	US / ED Aug 2012–Jan 2013	Cohort study III-2	Adults who had a cardiac arrest in the ED ($n = 65$)	Pharmacist present during resuscitation attempt ($n = 20$)	Pharmacist not present for resuscitation ($n = 45$)
Acquisto 2012 [32]	US / ED Aug 2005–Aug 2006	Cohort study III-2	STEMI presenting to ED, requiring urgent cardiac catheterisation ($n = 120$)	Pharmacist present during STEMI management (working hours) ($n = 68$)	Pharmacist not present (outside working hours) ($n = 52$)
Feih 2017 [50]	US / inpatients Aug–Oct 2012 Mar–May 2013	Historical control study III-3	Adult inpatients who experienced an RRT event ($n = 391$)	Pharmacist involvement on the RRT ($n = 157$)	Pre-implementation of pharmacist role ($n = 234$)
Alarfaj 2018 [43]	US / ED March 2014–Oct 2015	Cohort study III-2	Adults in ED with bleeding. Subgroup of patients who received PCC ($n = 60$)	Pharmacist present during working hours ($n = NR$)	Pharmacist not present (outside working hours) ($n = NR$)
Corio 2018 [47]	US / ED Sept 2015–Feb 2017	Historical control study III-3	Adults with confirmed ICH, documented warfarin use and INR>/= 2 ($n = 48$)	Pharmacist driven warfarin reversal protocol ($n = 24$)	Pre-implementation of pharmacist driven protocol ($n = 24$)
Imanaka 2020 [55]	Japan / ED ICU Dec 2017–May 2019	Cohort study III-2	Adults who received 4F-PCC due to major bleeding or urgent surgical/invasive procedures ($n = 10$)	Emergency ICU pharmacist intervention on weekdays ($n = 5$)	Emergency ICU pharmacist absent (on weekends) ($n = 5$)
Kozlow 2021 [58]	US / ED May 2014–June 2015. Nov 2018–Dec 2019	Historical control study III-3	Adults who received 4F-PCC in the ED for acute rapid reversal of oral anticoagulation due to bleeding ($n = 100$)	Pharmacist presence at the bedside to assist with anticoagulant reversal ($n = 67$)	Pharmacist not present (prior to 24 h EM pharmacist service) ($n = 33$)
Masic 2019 [60]	US / ED 2014–2018	Cohort study III-2	Adults who received 4F-PCC for life-threatening bleeding or urgent procedure in the ED ($n = 116$)	Pharmacist presence at the bedside to assist with anticoagulant reversal ($n = 50$)	Pharmacist not present ($n = 66$)
Amini 2013 [44]	US / ED July 2009–June 2011	Cohort study III-2	Adult trauma intubated using RSI and rocuronium in the ED ($n = 100$)	Pharmacist present during intubation within working hours ($n = 30$)	Pharmacist not present (outside working hours) ($n = 70$)
Ernst 2012 [49]	US /ED Jan–Apr 2009	Historical control study III-3	Adults presenting to the resuscitation and trauma areas ($n = 694$)	Presence of a pharmacist during 10 h working day ($n = 242$)	Pharmacist not present ($n = 452$)
Harvey 2018 [53]	US / ED May 2014–June 2016	Cohort study III-2	Adult trauma alert with fractures who presented to ED ($n = 146$)	Pharmacist present during trauma response (when available within working hours) ($n = 67$)	Pharmacist not present (after hours or not available)
Johnson 2015 [57]	US / ED Oct 2009–Dec 2012	Cohort study III-2	Adults intubated in the ED who received rocuronium or succinylcholine ($n = 106$)	Pharmacist present during intubation ($n = 72$)	Pharmacist not present during intubation ($n = 34$)
Lamkin 2019 [59]	US / ED July 2014–December 2014	Cohort study III-2	Adults who presented to the critical care area of ED with trauma on weekdays ($n = 1082$)	Pharmacist present during trauma response within working hours ($n = 782$)	Pharmacist not present (outside working hours) ($n = 300$)
Montgomery 2015 [62]	US / ED Jan 2009–May 2013	Cohort study III-2	Adult trauma alert activations who received IV hydromorphone, fentanyl or	Pharmacist present during trauma team response ($n = 170$)	Pharmacist not present during trauma team response

(continued on next page)

Table 1 (*continued*)

Author, Year Published	Country/Setting Study duration	Study design (level of evidence)[a]	Patient population (*n*)	Intervention group (*n*)	Control group (*n*)
			morphine ($n = 340$)		($n = 170$)
Riley 2013 [65]	US / ED Dec 2009–Nov 2010	Cohort study III-2	All priority 1 or 2 trauma alert patients in ED ($n = 538$)	Pharmacist present during trauma response ($n = 167$)	Pharmacist not present during trauma response ($n = 371$)
Robey-Gavin 2016 [66]	US / ED Jan-June 2010, Jan-June 2011	Historical control study III-3	Adults who had undergone RSI in the ED ($n = 82$)	Post implementation pharmacist service and presence ($n = 41$)	Pre-implementation of pharmacist service and presence ($n = 41$)
Chanas 2019 [46]	US / ICU Sept 2016–Mar 2017	Cohort study III-2	Septic shock in a surgical ICU ($n = 97$)	Pharmacist response to alert and bedside attendance ($n = 58$)	Pharmacist did not respond ($n = 39$)
Roman [71] 2023	Aus / ED Pre: Jan 2015 to Feb 2016 Post: 8 Feb 2016 to Feb 2018	Cohort study III-3	Adults with sepsis or septic shock requiring transfer to ICU within pharmacist working hours ($n = 184$)	Post implementation of pharmacist led sepsis alert response system ($n = 104$)	Pre- implementation of sepsis alert response ($n = 80$)
Tarabichi 2021 [70]	US / ED Aug–Dec 2019	Randomised controlled trial II	Adults for whom a sepsis flag triggered during their ED encounter ($n = 598$)	Sepsis score triggered: 1) icon on ED patient tracking tool 2) message to EMR monitored by pharmacist ($n = 285$)	Standard sepsis care ($n = 313$)
Gawedzki 2022 [69]	US / ED Jan 2018–July 2020	Cohort study III-2	Adults with status epilepticus in ED ($n = 20$)	Pharmacist present during status epilepticus management ($n = 13$)	Pharmacist not present ($n = 7$)

[a] As graded by the authors of this review according to the Australian National Health and Medical Research Council Designation of Levels of Evidence hierarchy, in which evidence is graded on 4 levels; AIS, acute ischemic stroke; Aus = Australia; CPR, cardiopulmonary resuscitation; ED, emergency department; EMR = electronic medical record; ICH, intracranial haemorrhage; ICU, intensive care unit; INR, international normalised ratio; IV, intravenous; NR, not reported; RSI, rapid sequence intubation; r-TPA = recombinant tissue plasminogen activator; RRT, rapid response team; STEMI, ST-segment elevation myocardial infarction; US, United States; 4F-PCC, four-factor prothrombin complex concentrate.

[42,44,46,50,51,60] which included inpatient settings. There was only one randomised controlled trial (RCT) [66], with the other non-randomised studies using a variety of methods to determine intervention and comparator groups. In 14 studies [28,39-41,45,47,49,51,52,55,56,60,61,65] the intervention group was determined by the pharmacists' usual working hours and a corresponding comparator group was selected outside of pharmacist working hours. The patient populations across studies varied widely. The impact of a pharmacist on acute stroke management was investigated in 8 studies [41,47,48,52,59,60,63,64] and on the management of haemorrhage requiring anticoagulant reversal in 5 studies [39,43,51,54,56]. Other patient cohorts included cardiac arrest [44,50,57] and rapid response teams [46] in 4 studies and STEMI management in one [28]. There were 8 studies [40,45,49,53,55,58,61,62] that investigated the involvement of EM pharmacists in major trauma and resuscitation response, 3 studies [42,66,67] in the management of sepsis and 1 in status epilepticus [65].

3.3. Outcomes

The results reported across the 30 studies are detailed in Table 2. Twenty-five studies compared the difference in time to administration of time critical medications between the control and intervention groups, but there were a variety of other outcomes assessed, such as medication error and appropriateness and length of stay (LOS). As shown in Table 3, the populations studied were grouped into 8 patient cohorts and the outcomes reported were divided into 8 categories. The table provides an overview of the key outcomes measured and whether the results were statistically significant for each category. Time to medication administration was commonly reported ($n = 25$). The remaining study outcomes measured were: appropriate medication use or medication error ($n = 10$); mortality ($n = 11$), including in-hospital mortality, 90 day mortality and survival to admission or discharge; hospital or ICU LOS ($n = 9$); guideline compliance ($n = 8$); efficacy measures ($n = 6$), which included 24 h or discharge National Institute of Health Stroke Scale (NIHSS) scores and change in pain score; adverse events ($n = 7$); and other patient outcomes ($n = 7$), which included admission to ICU, time on ventilator, discharge disposition to home, days alive and out of hospital, 90 day modified rankin scale (mRS) or NIHSS scores.

Time to medication administration was an outcome reported in six of the eight patient cohorts. Administration of time-critical medicines was expedited when a pharmacist was present for a range of medication classes including thrombolytic agents, prothrombin complex concentrate, sedating agents, analgesics, and antibiotics. Three studies [48,52,63] were powered to detect a difference in the median time from ED arrival to thrombolysis initiation when a pharmacist was present during an acute stroke response with all finding a significant improvement. These studies did not find a significant difference in the proportion of patients with an arrival to thrombolysis administration times of <60 min (Table 2), however a multivariate logistic regression (MVLR) performed by Jacoby [52] showed that involvement of an EM pharmacist was independently associated with an increased likelihood of receiving recombinant tissue plasminogen activator within 45 min. Similarly, Corio [43] and Masic [56] were powered to detect a reduction in the time to administration of 4 factor prothrombin complex concentrate (4F-PCC) when a pharmacist was present and reported statistically significant differences between the groups. The MVLR by Masic [56] found that a pharmacist at the bedside was the only factor independently associated with a reduced time to 4F-PCC administration. Chanas [42], Roman [67] and Tarabichi [66] demonstrated a statistically significant reduction in time to antibiotic administration, whereas Lamkin [55] did not.

Ernst [45] found that significantly fewer patients experienced a ME when a pharmacist was present. In this study, the proportion of patients with a ME was reduced from 30.3% to 2.5%, across the total patient population and from 48.6% to 7.7% for the subgroup of critically ill patients admitted to ICU. The studies by Harvey, Lamkin, Riley and Robey-Gavin [49,55,61,62] found that antibiotics, sedatives and analgesics were significantly more likely to be used appropriately or according to guidelines during major trauma resuscitation when a pharmacist was present. A pharmacist led sepsis alert intervention improved the proportion of patients receiving the entire bundle of sepsis care within 60 min of arrival (including intravenous fluids, two sets of blood cultures, serum lactate and empiric antimicrobials) as recommended the Surviving Sepsis Campaign and national guidelines [67]. In status epilepticus, Gawedzki [65] found that the presence of a pharmacist led to higher median total lorazepam equivalents administered. Pharmacists on cardiac arrest teams improved compliance with resuscitation guidelines with all three studies in this patient cohort [44,50,57] reporting

Table 2
Summary of outcomes, results, and statistical significance

Author, Year Published, Patient Cohort, Number (n)	Outcomes	Results (Intervention vs Control)	Method of statistical analysis	*p*-value, 95% CI (if presented)
Barbour 2022 [45]	P: Median alteplase DTN time, min (IQR)	35 (29–44) vs 42 (34–55)	MWU test	$p = 0.025$
Acute stroke	S: Patients with DTN time ≤ 60 min, %	93.6 vs 81.9, OR 3.19	χ^2 test	$p = 0.111$, 0.71–14.3
$n = 164$	S: Patients with DTN time ≤ 45 min, %	80.7 vs 57.1, OR 3.13	χ^2 test	$p = 0.015$, 1.20–8.12
	S: Patients with DTN time ≤ 30 min, %	35.5 vs 16.5, OR 2.78	χ^2 test	$p = 0.018$, 1.17–6.60
	S: Median NIHSS at 24 h, score (IQR)	3 (1–9) vs 6 (2−11)	FE test	$p = 0.087$
	S: Median NIHSS at discharge, score (IQR)	2 (0–5) vs 4 (0.25–8.75)	FE test	$p = 0.049$
	S: Median hospital LOS, days (IQR)	3 (2–5) vs 4 (3–4)	MWU test	$p = 0.063$
Gilbert 2019 [51]	P: Patients with DTN time ≤ 60 min, *n* (%)	26 (78.8) vs 17 (53.1), OR 3.3	χ^2 test	$p = 0.04$, 1.1–9.6
Acute stroke	S: Median DTN time, min (range)	47 (22–74) vs 60 (36–109)	WRS test	$p = 0.001$
$n = 65$	S: Mean DTN time, min (range)	49 (22–74) vs 63 (36–109)	WRS test	$p = 0.003$
Gosser 2016 [52]	P: Median DTN time, min (IQR)	69.5 (59–87.5) vs 89.5 (70–104)	MWU test	$p = 0.0027$
Acute stroke	S: Patients with a DTN time ≤ 60 min, *n* (%)	20 (29.9) vs 6 (15.8)	χ^2 test	$p = 0.1087$
$n = 105$	S: Appropriate thrombolysis dose, %	96.6 vs 95.6	Student's *t*-test	$p = 0.8953$
Jacoby 2018 [56]	P: Median DTN time, min (IQR)	46 (34.5–67) vs 58 (45–79)	MWU test	$p = 0.019$
Acute stroke	S: Patients with a DTN time ≤ 45 min, *n* (%)	24 (49) vs 13 (25), OR 2.81	χ^2 test	$p = 0.015$, 1.21–6.52
$n = 100$	S: Patients with a DTN time ≤ 60 min, *n* (%)	35 (71) vs 31 (61), OR 1.61	χ^2 test	$p = 0.261$, 0.70–3.72
	S: Median NIHSS at 24 h, score (IQR)	1 (0–4) vs 2 (1–9.25)	MWU test	$p = 0.047$
	S: Median NIHSS at discharge, score (IQR)	0 (0–4) vs 2 (0–6)	MWU test	$p = 0.077$
	S: Median NIHSS at follow up, score (IQR)	0 (0–2) vs 1 (0–5.5)	MWU test	$p = 0.198$
	S: Symptomatic ICH, number of events	3 vs 2	FE test	$p = 0.068$
	S: Hospital LOS, days (IQR)	2.6 (1.8–3.9) vs 2.9 (2.0–4.0)	MWU test	$p = 0.500$
	S: Patients discharged to home, *n* (%)	30 (65) vs 26 (54)	FE test	$p = 0.384$
McSwain 2022 [68]	P: Mean DTN time, min (SD)	66 (27) vs 78 (38)	Welch's t-test	$p = 0.038$
Acute stroke	S: Patients with DTN time < 60 min, *n* (%)	24 (60) vs 41 (34), OR 2.85	FE test	$p = 0.05$, 1.37–5.96
$n = 159$	S: Patients with DTN time < 45 min, *n* (%)	7 (18) vs 24 (20), OR 0.83	FE test	$p = 0.71$, 0.33–2.13
Montgomery 2016 [63]	P: Patients with DTN time < 60 min, *n* (%)	27 (71) vs 23 (39)	χ^2 test	$p = 0.002$, 0.10–0.50
Acute stroke				
$n = 97$	S: Patients with DTN time < 45 min, *n* (%)	16 (42) vs 11 (19)	χ^2 test	$p = 0.012$, 0.05–0.41
	S: Mean DTN time, min (range)	54 (21–160) vs 74 (28–187)	Student's *t*-test	$p = 0.004$, 6.6–33.4
Rech 2017 [64]	P: Median DTN time, min (IQR)	48 (36–65) vs 73 (58–97.5)	MWU test	$p < 0.01$
Acute stroke	S: Patients with DTN time ≤ 60 min, *n* (%)	32 (71.1) vs 23 (28.8)	χ^2 test	$p < 0.01$
$n = 125$	S: Patients with DTN time ≤ 45 min, *n* (%)	20 (44.4) vs 7 (8.8)	χ^2 test	$p < 0.01$
	S: Median door to imaging, min (IQR)	16 (10−21) vs 16 (8–25)	MWU test	$p = 0.85$
	S: Median imaging to needle time, min (IQR)	28 (22–42.5) vs 55.5 (42–70.5)	MWU test	$p < 0.01$
	S: ICU LOS, days (IQR)	3 (2–9) vs 2 (2–4) days	MWU test	$p = 0.06$
	S: Hospital LOS, days (IQR)	6 (3−13) vs 4 (3–8)	MWU test	$p = 0.09$
	S: Hospital mortality, *n* (%)	5 (11.1) vs 9 (11.3)	χ^2 test	$p = 0.98$
	S: 90 day mortality, *n* (%)	10 (22.2) vs 12 (15)	χ^2 test	$p = 0.32$
	S: Median discharge mRS, score (IQR)	3 (0–5) vs 3 (1–4)	FE test	$p = 0.85$
	S: Median 90 day mRS, score (IQR)	2 (0–4) vs 2 (1–4)	FE test	$p = 0.84$
	S: Discharge NIHSS, score (IQR)	3 (0−11) vs 4 (0−10)	FE test	$p = 0.71$
	S: Median 90 day NIHSS (IQR)	0 (0–0) vs 5 (0–5)	FE test	$p = 0.05$
	S: Patients with symptomatic haemorrhage, *n* (%)	5 (11.1) vs 6 (7.6)	χ^2 test	$p = 0.51$
Roman 2021 [67]	P: Median DTN time, min (IQR)	61 (47–80) vs 73 (52–111)	WRS test	$p = 0.012$
Acute stroke	S: Patients with DTN time of <60 min, *n* (%)	59 (48.4) vs 22 (34.4)	OLSR	$p = 0.068$
$n = 186$	S: Median time from CTB to rtPA, min (IQR)	39 (28–56) vs 50.5 (30.5–79)	WRS test	$p = 0.013$
	S: Median hospital LOS, days (IQR)	4.2 (2.9–7.3) vs 6.6 (4.1–10.8)	WRS test	$p = 0.003$
	S: Hospital mortality, *n* (%)	24 (19.7) vs 12 (18.8)	OLSR	$p = 0.97$
	S: Extracranial haemorrhage, *n* (%)	5 (4.1) vs 7 (10.9)	OLSR	$p = 0.07$
	S: Patients with ICH, *n* (%)	17 (13.9) vs 7 (10.9)	OLSR	$p = 0.40$
Draper 2008 [48] Cardiac arrest	Arrests compliant with ACLS guidelines, %	59.3 vs 31.9	χ^2 test	$p = 0.03$
	Arrests with non-compliant medication interventions, *n* (%)	15 (32.6) vs 31 (67.4)	NR[a]	NR[a]
$n = 74$				
Heavner 2017 [54]	Arrest events with all documentation complete, %	28 vs 0	χ^2 test	$p = 0.002$
Cardiac arrest	Events compliant with ACLS guidelines, %	31 vs 8	χ^2 test	$p = 0.024$
$n = 80$	Patients who survived the acute event, %	59 vs 58	χ^2 test	Not significant
McAllister 2017 [61]	P: Medication compliance with ACLS guidelines, *n* (%)	93 (78) vs 154 (67)	χ^2 test	$p = 0.0255$
Cardiac arrest	S: Guideline compliance: defibrillation, *n* (%)	23 (68) vs 8 (47)	χ^2 test	$p = 0.1557$
$n = 65$	S: Guideline compliance: composite measure, *n* (%)	116 (76) vs 162 (65)	χ^2 test	$p = 0.0268$
	S: Resuscitation events compliant with ACLS guidelines, *n* (%)	9 (43) vs 14 (27)	χ^2 test	$p = 0.2000$
	S: Survival to hospital admission, *n* (%)	8 (25) vs 5 (17.8)	FE test	$p = 0.0155$
	S: Survival to hospital discharge, *n* (%)	2 (15) vs 3 (4.4)	FE test	$p = 0.6392$
Acquisto 2012 [32]	Change in mean time from arrival/diagnosis to CCL, min	−13.1	MV OLSR	$p = 0.0324$,

(continued on next page)

Table 2 (*continued*)

Author, Year Published, Patient Cohort, Number (n)	Outcomes	Results (Intervention vs Control)	Method of statistical analysis	*p*-value, 95% CI (if presented)
STEMI				6.5–21.9
$n = 120$	Change in mean time from arrival/diagnosis to angioplasty, min	−11.5	MV OLSR	$p = 0.0487$, 3.9–21.5
	Arrival/ diagnosis to CCL of ≤30 min with pharmacist present	OR = 3.1	MV OLSR	1.3–7.8
	Arrival/diagnosis to CCL time ≤ 45 min with pharmacist present	OR = 2.9	MV OLSR	1.0–8.5
	Arrival/diagnosis to angioplasty ≤90 min when pharmacist present	OR = 1.9	MV OLSR	0.7–5.5
Feih 2017 [50]	P: Median time from order entry to administration, min	32.0 vs 64.5	WRS test	$p = 0.004$
Rapid response team	P: Patients administered medication within 30 min, %	53.8 vs 22.2	χ^2 test	$p = 0.015$
$n = 391$	S: Patients admitted to ICU	NR[a]	χ^2 test	Not significant[b]
	S: ICU readmission <48 h of discharge	NR[a]	χ^2 test	Not significant[b]
	S: Hospital LOS	NR[a]	WRS test	Not significant[b]
	S: Survival to discharge	NR[a]	χ^2 test	Not significant[b]
Alarfaj 2018 [43]	Median time from order to PCC administration, min (IQR)	24 (15–35) vs 42 (32–59)	WRS test	$p < 0.001$
Haemorrhage				
$n = 60$				
Corio 2018 [47]	P: Median diagnosis to 4F-PCC administration time, min (IQR)	35 (25–62) vs 70 (34–89)	MWU	$p = 0.034$
Haemorrhage	S: Patients with appropriate dose of 4F-PCC, *n* (%)	23 (95.8) vs 20 (83.3)	FE test	$p = 0.174$
$n = 48$	S: Patients administered concomitant vitamin K, *n* (%)	24 (100) vs 22 (91.7)	FE test	$p = 0.244$
	S: In-hospital mortality, *n* (%)	7 (29.2) vs 7 (29.2)	FE test	$p = 1$
Imanaka 2020 [55]	Median ICU arrival to 4F-PCC administration time, min (range)	103 (41–144) vs 111 (70–203)	MWU	$p = 0.4$
Haemorrhage	Median 4F-PCC prescription to administration time, min (range)	21 (5–39) vs 60 (33–157)	MWU	$p = 0.02$
$n = 10$				
Kozlow 2021 [58]	P: Mean order entry to administration of 4F-PCC time, min (SD)	35.2 (14.4) vs 71.2 (31.0)	MWU	$p < 0.001$, 27.0–45.0
Haemorrhage				
$n = 100$	S: Median ED arrival to administration of 4F-PCC time, min (IQR)	106 (66–142) vs 153 (89–205)	MWU	$p = 0.033$
	S: Hospital LOS, days (IQR)	4.1 (2.8–5.8) vs 6.9 (3.6–9.8)	MWU	$p = 0.017$
	S: ICU admission, *n* (%)	10 (30.3) vs 43 (64.2)	χ^2 test	$p = 0.003$
	S: ICU LOS, days (IQR)	1.6 (0.83–3.4) vs 2.2 (0.79–2.9)	MWU	$p = 0.75$
	S: Admission mortality, *n* (%)	4 (12.1) vs 10 (14.9)	χ^2 test	$p = 1.0$
Masic 2019 [60]	P: Median ED arrival to 4F-PCC administration time, min (IQR)	66.5 (37.5–95.5) vs 206.5 (88–325)	MWU	$p < 0.01$
Haemorrhage	S: Achievement of haemostasis, *n* (%)	29 (87.8) vs 38 (84.4)	χ^2 test	$p = 0.67$
$n = 116$	S: Packed red blood cells within 24 h of 4F-PCC, mean (SD)	0.11 (0.4) vs 0.06 (0.3)	χ^2 test	$p = 0.53$
	S: Platelets <24 h of 4F-PCC, mean (SD)	0.15 (0.5) vs 0.38 (0.7)	χ^2 test	$p = 0.25$
	S: Fresh frozen plasma within 24 h of 4F-PCC, mean (SD)	0.20 (0.6) vs 0.56 (1)	χ^2 test	$p = 0.04$
	S: Patients given appropriate 4F-PCC dose, *n* (%)	48 (96) vs 61 (92.4)	χ^2 test	$p = 0.42$
	S: Safety outcomes	Multiple reported	χ^2 test	Not significant[b]
	S: Discharge disposition home, *n* (%)	19 [38] vs 13 [19.7]	χ^2 test	$p = 0.03$
	S: ICU LOS, days (IQR)	2 (1–3) vs 5 (1–9)	MWU	$p < 0.01$
	S: Hospital LOS, days (IQR)	5.5 (2.5–8.5) vs 8 (2.5–13.5)	MWU	$p = 0.02$
	S: 30-day mortality, *n* (%)	11 [22] vs 14 [21.2]	χ^2 test	$p = 0.55$
Amini 2013 [44]	Mean time to postintubation sedation, min (SD)	9 (± 12) vs 28 (± 29)	Student's *t*-test	$p < 0.007$
Major trauma resuscitation	Mean time to postintubation analgesia, min (SD)	21 (± 24) vs 44 (± 47)	Student's *t*-test	$p = 0.057$
$n = 100$				
Ernst 2012 [49]	P: Total patients ($n = 694$) with medication error, *n* (%)	6 (2.5) vs 137 (30.3), OR 17.1	χ^2 test	7.4–39.4
Major trauma resuscitation	ICU admitted patients ($n = 157$) with medication error, *n* (%)	4 (7.7) vs 51 (48.6), OR 6.8	χ^2 test	3.7–12.7
$n = 694$	Non-ICU admitted patient ($n = 200$) with medication error, *n* (%)	2 (5.1) vs 53 (32.5), OR 3.6	χ^2 test	1.9–6.5
	Patients transferred to operating room with medication error, *n* (%)	1 (0.4) 6 vs (37.5), OR 3.8	χ^2 test	1.3–11.2
	Patients transferred to the ED observation area ($n = 40$) with medication error, *n* (%)	9 (22.5) vs 0 (0), OR 2.5	χ^2 test	1.0–6.3
Harvey 2018 [53]	P: Patients with initial AB prophylaxis guideline compliant, *n* (%)	54 (81) vs 37 (47)	χ^2 test	$p < 0.01$
Major trauma resuscitation	S: Median ED arrival to AB administration time, min (IQR)	14 (11−20) vs 20 (12–27)	Student's *t*-test	$p = 0.02$
$n = 146$				
Johnson 2015 [57]	P: Mean time to sedation or analgesia after NMBA facilitated RSI, min (SD)	20 (21) vs 49 (45)	Student's *t*-test	$p < 0.001$
Major trauma resuscitation				
$n = 106$				
	P: Mean time to sedation or analgesia after rocuronium facilitated RSI, min (SD)	23 (22) vs 55 (46)	Student's *t*-test	$p = 0.002$
	P: Mean time to sedation/analgesia after succinylcholine facilitated RSI, min (SD)	13 (14) vs 28 (3)	Student's *t*-test	$p = 0.306$
Lamkin 2019 [59]	P: Median time to AB, min (IQR)	20 (12–29) vs 18 (9–27)	WRS test	$p = 0.39$
Major trauma resuscitation	P: Median time to RSI, min (IQR)	12.5 (6–18) vs 12 (10−22)	WRS test	$p = 0.78$
$n = 1082$	P: Median time from RSI to sedation, min (IQR)	7.5 (5–16) vs 8 (0–10)	WRS test	$p = 0.50$
	P: Median time to analgesia, min (IQR)	11 (8–27) vs 13 (8.5–20)	WRS test	$p = 0.047$
	P: Median time to anticoagulation reversal	Nil		
	S: Patients receiving appropriate AB, *n* (%)	46 (80.7) vs 12 (52.2)	FE test	$p = 0.01$
	S: Patients given tetanus vaccination, *n* (%)	160 (20.5) vs 56 (18.7)	FE test	$p = 0.55$

Table 2 (*continued*)

Author, Year Published, Patient Cohort, Number (n)	Outcomes	Results (Intervention vs Control)	Method of statistical analysis	*p*-value, 95% CI (if presented)
Montgomery 2015 [62]	P: Mean time from arrival to analgesic administration, min	17 vs 21	Student's *t*-test	$p = 0.03$
Major trauma resuscitation	S: Mean change in pain score from trauma bay arrival to ED transfer, pain score change	−2.4 vs −2.8	MWU	$p = 0.57$
$n = 340$	S: Mean time from prehospital to first ED analgesic, min	29.9 vs 32	Student's *t*-test	$p = 0.68$
Riley 2013 [65]	Patients in whom an AB was given, *n* (%)	80 (48) vs 105 (28.3)	χ^2 test	$p = 0.0003$
Major trauma resuscitation	Patients given appropriate AB, *n* (%)	70 (87.5) vs 83 (78)	χ^2 test	$p = 0.132$
$n = 538$	Patients given appropriate AB dose, *n* (%)	79 (99) vs 83 (79)	χ^2 test	$p = 0.00006$
	Patients with AB omission, *n* (%)	1 (1.23) vs 76 (20.5)	χ^2 test	$p \leq 0.00001$
	Mean time from arrival to AB administration, min (SD)	17.7 (18.9) vs 36.6 (38.9)	Student's *t*-test	$p = 0.01$
Robey-Gavin 2016 [66]	P: Patients given analgesia post RSI, %	49 vs 20	χ^2 test	$p = 0.005$
Major trauma resuscitation	S: Patients given sedation without analgesia, %	51 vs 73	χ^2 test	$p = 0.04$
$n = 82$	S: Time to initiation of postintubation analgesia, min	45 vs 98	χ^2 test	Not stated
	S: Adverse drug events with discontinuation of analgesia, n	1 vs 0	χ^2 test	Not stated
Chanas 2019 [46]	Time from advisory trigger to AB administration; h	1.2 vs 4.2	Kruskal-Wallis	$p = 0.046$
Sepsis	Patients administered AB <1 h, *n* (%)	9 (36) vs 8 (14)	χ^2 test	$p = 0.021$
	Patients administered AB <3 h, *n* (%)	15 (60) vs 20 (34)	χ^2 test	$p = 0.031$
Roman 2023 [71]	P: Patients given AB <60 min arrival, *n* (%)	85 (81.7) vs 21 (26.3)	NR[c]	$p \leq 0.001$
Sepsis	S: Median time to antibiotics, min (IQR)	38 (27–54) vs 91 (59.5–163.5)	NR[c]	p ≤0.001
$n = 184$		75 (72.1) vs 38 (47.5)		
	S: Patients given fluids within 60 min, *n* (%)	81 (77.9) vs 40 (50.0)	NR[c]	$p = 0.002$
	S: Serum lactate <60 min, *n* (%)	89 (85.6) vs 42 (52.5)	NR[c]	p ≤0.001
	S: Blood cultures taken <60 min, *n* (%)	71 (68.9) vs 60 (75.0)	NR[c]	p ≤0.001
	S: Blood cultures taken before ABs, *n* (%)	52 (50.0) vs 8 (10.0)	NR[c]	$p = 0.37$
	S: All four indicators within 60 min, *n* (%)	6 (5–8.5) vs 6 (4–8)	NR[c]	p ≤0.001
	S: Median LOS in ED, h (IQR)	82 (50.5–143.5) vs 82.5 (40–120)	NR[c]	$p = 0.45$
	S: Median LOS in ICU, h (IQR)	15 (14.4) vs 9 (11.2)	NR[c]	$p = 0.24$
		269.5 (162.5–487.5) vs 234.5		
	S: Death at hospital discharge, *n* (%)	(142–463)	NR[c]	$p = 0.27$
	S: Median LOS in hospital, h (IQR)		NR[c]	$p = 0.36$
Tarabichi 2021 [70]	P: Median ED arrival to AB administration time; h (IQR)	2.3 (1.4–4.7) vs 3 (1.6–5.5)	WRS test	$p = 0.039$
Sepsis	P: Median days alive and out of hospital at 28 days; days	24.1 vs 22.5	WRS test	$p = 0.011$
$n = 598$	S: Median length of stay; days (IQR)	3.2 (1.1–6.2) vs 4.0 (1.4–7.0)	WRS test	$p = 0.124$
	S: Hospital mortality, *n* (%)	13 (4.6) vs 25 (8.0)	χ^2 test	$p = 0.086$
	S: 28-day mortality, *n* (%)	17 (6.0) vs 31 (9.9)	χ^2 test	$p = 0.077$
	S: AB utilisation; *n* (%)	193 (67.7) vs 219 (70.0)	χ^2 test	$p = 0.553$
	S: Fluid bolus administration; *n* (%)	174 (61.1) vs 203 (64.9)	χ^2 test	$p = 0.336$
	S: Median fluid volume by weight; mL/kg (IQR)	39.1 (23.9–62.2) vs 41.0 (22.5–64.2)	WRS test	$p = 0.831$
	S: *Clostridiodes difficile* diagnosis; *n* (%)	2 (0.7) vs 5 (1.6)	χ^2 test	$p = 0.309$
	S: Admitted to inpatient setting; *n* (%)	217 (76.1) vs 254 (81.2)	χ^2 test	$p = 0.135$
	S: Admission to ICU; *n* (%)	101 (35.4) vs 128 (40.9)	χ^2 test	$p = 0.170$
	S: Median ICU length of stay; days (IQR)	3.6 (2.0–5.4) vs 3.4 (2.0–6.0)	WRS test	$p = 0.937$
	S: 28-day ED/hospital representation, *n* (%)	70 (24.6) vs 96 (30.7)	χ^2 test	$p = 0.09$
Gawedzki 2022 [69]	P: Median time from ED arrival to antiepileptic administration, min (IQR)	1st: 26 (17–177) vs 37 (21–206)	WRS test	$p = 0.58$
Status epilepticus		2nd: 51 (30—221) vs 171 (99–433)		$p = 0.07$
$n = 20$		3rd: 205 (96–416) vs 335 (0)		$p = 0.69$
	S: Proportion of patients who received an appropriate antiepileptic	1st: 11 (85) vs 7 (100)	χ^2 test	$p = 0.52$
		2nd: 11 (92) vs 4 (80)	FE test	$p = 0.54$
	for each antiepileptic selected, *n* (%)	3rd: 7 (88) vs 1 (100)		$p = 1$
	S: Patients who received an appropriate dose for each antiepileptic,	1st: 3 (23) vs 0	χ^2 test	$p = 0.52$
		2nd: 3 (25) vs 1 (20)		$p = 1.0$
	n (%)	3rd: 4 (50) vs 0		$p = 1.0$
	S: Median lorazepam equivalent, mg (IQR)	2.5 (2–4) vs 2 (0)	WRS test	$p = 0.04$
	S: Received >/= 4 mg of lorazepam equivalents, *n* (%)	5 (38) vs 0	χ^2 test	$p = 0.11$
	S: Intubated in ED, *n* (%)	1 (8) vs 0	χ^2 test	1
	S: Refractory status epilepticus, *n* (%)	1 (8) vs 0	χ^2 test	1
	S: 30-day mortality, *n* (%)	1 (8) vs 0	χ^2 test	1
	S: ICU admission, *n* (%)	7 (54) vs 0	χ^2 test	$p = 0.04$
	S: Median ED LOS, min (IQR)	431 (340–568) vs 679 (570–992)	WRS test	$p = 0.006$
	S: Median Hospital LOS, days (IQR)	3 (2–9) vs 3 (1–4)	WRS test	$p = 0.18$

p = primary outcome; S = secondary outcome. [a]NR = not reported: predetermined end point for which details of results and analysis were not reported in the published paper. [b]Statistical analysis of outcome reported in published paper qualitatively only. [c]NR = not reported: specific statistical test used not reported in published paper. AB, antibiotic; ACLS, acute cardiac life support; AIS, Acute ischemic stroke; CCL, cardiac catheter laboratory; CPR, cardiopulmonary resuscitation; CTB, computed tomography; DTN, door to needle time; ED, emergency department; EMR, electronic medical record; FE, Fisher's Exact; ICH, intracranial haemorrhage; ICU, intensive care unit; IQR, interquartile range; 4F-PCC, four-factor prothrombin complex concentrate; KW, Kruskal-Wallis; LOS, length of stay; mRS, modified Rankin score; MWU, Mann-Whitney U; NIHSS, national institute of health stroke score; MV OLSR, multivariate ordinary least squares regression; NMBA, neuromuscular blocking agent; r-TPA, recombinant tissue plasminogen activator; STEMI, ST-segment elevation myocardial infarction, WRS, Wilcoxon Rank Sum; χ^2 = Chi-square.

Table 3
Summary of outcomes assessed for each patient cohort.

Patient Cohort, Publication and Setting	Setting	Time to administration	Medication error / Appropriate use	Hospital or ICU LOS	Mortality	Efficacy measure	ADE	Guideline compliance	*Other Patient Outcome
Acute stroke									
Barbour 2022[45]	ED	✔	-	⊘	-	✔	-	-	-
Gilbert 2019[53]	ED	✔	-	-	-	-	-	-	-
Gosser 2016[52]	ED	✔	⊘	-	-	-	-	-	-
Jacoby 2018[56]	ED	✔	-	⊘	⊘	✔	⊘	-	⊘
Montgomery 2016[63]	ED	✔	-	-	-	-	-		-
McSwain 2022[68]	ED	✔	-	-	-	-	-	-	-
Rech 2017[64]	ED/Inpt	✔	-	⊘	⊘	⊘	⊘	-	✔
Roman 2021[67]	ED	✔	-	✔	⊘	-	✔	-	-
Cardiac arrest									
Draper 2008[48]	Inpt	-	✔	-	-	-	-	✔	-
Heavner 2017[54]	Inpt	-	-	-	⊘	-	-	✔	-
McAllister 2017[51]	ED	-	✔	-	✔	-	-	✔	-
STEMI									
Acquisto 2012[32]	ED	-	-	-	-	-	-	✔	-
RRT									
Feih 2017[50]	Inpt	✔	-	⊘	⊘	-	-	-	⊘
Acute severe haemorrhage									
Alfarfaj 2018[43]	ED	✔	-	-	-	-	-	-	-
Corio 2018[47]	ED	✔	-	-	-	-	-	-	-
Imanaka 2020[55]	ED	✔	-	-	-	-	-	-	-
Kozlow 2021[58]	ED	✔	-	✔	⊘	-	-	-	✔
Masic 2019[60]	ED	✔	⊘	✔	⊘	⊘	⊘	-	✔
Major trauma and resuscitation									
Amini 2013[44]	ED	✔	-	-	-	-	-	-	-
Ernst 2012[49]	ED	-	✔	-	-	-		-	-
Harvey 2018[53]	ED	✔	✔	-	-	-	-	✔	-
Johnson 2015[57]	ED	✔	-	-	-	-	-	-	-
Lamkin 2019[59]	ED	✔	✔	-	-	-	-	-	-
Montgomery 2015[62]	ED	✔	-	-	-	⊘	-	-	-
Riley 2013[65]	ED	✔	✔	-	-	-		✔	-
Robey-Gavin 2016[66]	ED	⊘	✔	-	-	-	-	✔	-
Sepsis									
Chanas 2019[46]	Inpt	✔	-	-	-	-	-	-	-
Roman 2023[71]	ED	✔	-	⊘	⊘	-	-	✔	-
Tarabichi 2021[70]	ED	✔	-	⊘	⊘	⊘	⊘	-	✔
Status epilepticus									
Gawedzki 2022[69]	ED	⊘	✔	⊘	⊘	-	⊘	-	⊘

✔ = Outcome was assessed, result was statistically significant.
⊘ = Outcome was assessed, result was not statistically significant.
– = Outcome was not assessed in this study.
ED = emergency department, ICU = intensive care unit, Inpt = inpatient, LOS = length of stay, STEMI = ST elevation myocardial infarction, RRT = rapid response team.
* Other Patient Outcome = admission to ICU, discharge disposition to home, days alive and out of hospital, 90-day modified Rankin Score or National Institute of Health Stroke Scale.

statistically significant improvements in compliance with ACLS guidelines. Acquisto [28] found that for patients requiring STEMI management, pharmacist presence reduced the mean time to the cardiac catheter lab and evaluation) and to balloon angioplasty initiation.

Statistically significant improvements in efficacy measures for stroke thrombolysis treatment such as median NIHSS at 24 h and NIHSS at discharge were shown in Jacoby and Barbour [41,52]. There were no differences in medication adverse event rates between groups for any of the included studies. Two acute stroke management and acute haemorrhage studies demonstrated shorter hospital or ICU LOS in the intervention groups [54,56,60,63]. Kozlow [54] showed that pharmacist involvement in acute haemorrhage management reduced ICU admission rates. Finally, one study demonstrated that significantly more patients survived to hospital admission when a pharmacist was included on the ED resuscitation team managing cardiac arrest [57].

3.4. Clinical heterogeneity

There was significant clinical heterogeneity between studies (see Tables 1 and 2). The models for pharmacist inclusion differed in terms of the setting, pharmacist roles and method of alert and response. Patient selection and outcomes differed according to the patient cohort of interest. Given these differences, we determined that a meta-analysis was not appropriate.

3.5. Risk of bias and quality assessment

A summary of the quality and RoB assessment of individual studies is displayed in Table 4 (supplement). Retrospective record review was the method of data collection in all but one of the cohort studies [45], which used a combination of retrospective record reviews and prospective data collection. Double data extraction was undertaken in 1 study [39]; variables for collection were explicitly defined in all but 3 studies [40,51,62]; 6 studies utilised a blinded outcome assessment [28,40,43,46,56,66]; and 11 studies [39,40,43,45,46,48,52,53,56,63,67] performed a power calculation to determine the sample size. Only 11 studies [28,39,41,45,47,48,52,56,60,63,67] assessed and controlled for confounding variables for the primary outcome by study design or using a statistical adjustment approach such as multivariate logistic regression, which reduced the quality and increased the overall risk of bias of the remaining studies. Tarabichi [66], the only RCT, was assessed as having a low RoB across the four domains of the RoB-2 tool. The NOS was scored out of a maximum of 9 points. Acquisto, Alarfaj, Jacoby, Masic, Rech, Roman 2021 and Roman 2023 [28,39,52,56,60,63,67] scored 8 or 9 on NOS and had at least one of the additional quality criteria included in their methods. A general limitation of the included studies was the inherent risk of bias due to a potential for over-reporting of pharmacist benefit as most of the studies were conducted to justify pharmacy services.

4. Discussion

This systematic review identified 30 studies that evaluated the impact of the presence of a pharmacist working within a resuscitation or medical emergency response team. We observed a positive impact of a pharmacist presence for a variety of cohorts including acute ischemic stroke, cardiac arrest, acute haemorrhage, major trauma, and sepsis. Pharmacist involvement demonstrated benefits across a range of outcomes including time to medication administration, medication appropriateness, efficacy measurements, medication error, hospital and ICU LOS, mortality, and guideline compliance. These results demonstrate that pharmacists have diverse roles within resuscitation and medical emergency teams across a range of patient cohorts. The studies where pharmacists assisted with the management of acute stroke [52,60,63], severe haemorrhage [39,56], sepsis [42,66,67] and trauma [53] demonstrated the most consistent benefits, especially in outcomes such as time to medication administration. However, the evidence was insufficient to determine the impact of the presence of a pharmacist on patient related outcomes such as mortality and LOS. The results were shown to be favourable in studies from only two of the eight cohorts (haemorrhage and stroke management). Unfortunately, all of the studies included were significantly underpowered to detect differences between groups for these patient related outcomes.

4.1. Key outcomes of included studies

Of the eight outcomes measured, the most frequently reported ($n = 24$) and associated with a statistically significant benefit in 22 studies was time to medication administration (Table 3). The outcomes represented in each patient cohort were disparate. Appropriate medication use had a preponderance of literature support in three of the eight patient cohorts (cardiac arrest, trauma and status epilepticus) and guideline compliance in two (cardiac arrest and STEMI) (Table 3). However, a benefit across these outcomes was demonstrated in <50% of studies in the major trauma and sepsis cohorts.

Involving pharmacists in resuscitation or medical emergency response teams was associated with a shortened time to administration of critical medications such as thrombolysis [41,47,48,52,59,60,63,64], 4-factor prothrombin complex concentrate [39,43,51,54,56], antibiotics [42,66] and analgesics [55,58]. International Stroke Guidelines recommend that thrombolysis be administered as early as possible after stroke onset [68-70]. as shorter time-to-thrombolysis in acute ischemic stroke is associated with improved functional outcome and reduced morbidity [71]. Tarabichi [66] found that the presence of a pharmacist significantly reduced time to antibiotics, and increased the number of patient days alive and out of hospital. When managing sepsis, a delay to the first dose of antimicrobial therapy is associated with increased mortality [72,73]. During acute severe haemorrhage management, significant differences in hospital and ICU admission, ICU LOS and discharge home was reported in studies which found a reduced time to 4F-PCC administration when a pharmacist was assisting [54,56]. Although there is no definitive evidence regarding the optimal timing of administration of 4F-PCC to maximise clinical outcomes, optimal haemostatic management significantly restricts haemorrhage progression in all types of intra-cranial haemorrhage associated with oral anticoagulants [74]. Although sample sizes in several studies were small and the data heterogeneous, these positive findings contribute to evidence that pharmacists should be involved in sepsis, stroke and acute critical bleeding resuscitation teams in hospitals.

Ernst [45] determined that the presence of a pharmacist reduced medication errors in the trauma and resuscitation area of an ED, with the most critically ill patients deriving the greatest benefit. Improved appropriateness of use of antibiotics such as beta-lactams and aminoglycosides, through better adherence to guidelines and appropriate dosing was demonstrated in three other studies of trauma patient cohorts [49,55,61]. Robey-Gavin [62] established that pharmacists also have an impact on ensuring adequate use of analgesics, for patients who had undergone rapid sequence intubation. Draper [75] and McAllister [57] found that pharmacists improve compliance with acute cardiac life support guidelines. These findings suggest that a pharmacist's presence at bedside during the fast-paced, acute resuscitation of critically ill patients can facilitate the safe and timely delivery of medications. It has been suggested that formal integration of a pharmacist into the team enables clinicians to focus on other critical aspects of patient care such as diagnosis and assessment, thereby improving the efficiency of the team and higher chance of a favourable patient outcome [19,30,31,76-78].

The addition of a pharmacist to acute stroke teams, sepsis management teams and during acute haemorrhage management, demonstrated positive impacts on hospital and ICU LOS and other patient related outcomes in these patient cohorts [54,56,60,63]. McAllister [57] was the only study to demonstrate a significant mortality benefit, specifically, an improvement in patient survival to hospital admission as a secondary outcome measure. Mortality was not a primary outcome in any of the included studies as they were not powered to demonstrate this benefit. In the ICU setting, a systematic review by Lee [79] found that including critical care pharmacists in the multidisciplinary team improved patient outcomes such as mortality, ICU LOS and adverse drug events. They proposed that ICU pharmacists may reduce the medication related workload of other clinicians, increasing their colleagues' ability to focus on other aspects of patient care. Further research is needed to determine if this effect can be demonstrated in other high-risk acute care settings such as ED resuscitation and trauma care.

4.2. Specific roles of the pharmacist

This review identified a wide range of EM pharmacist responsibilities during resuscitation and medical emergency response events.

These included retrieval of patient specific information [28,41,47,48,51,52,56,60-64], dose calculation or verification [28,39-41,43,45-49,51,52,54,55,59,60,62-64], obtaining and preparing medications [28,39-41,43,44,46-52,54,55,58-64,66], infusion pump programming [28,41,47], medication information and drug therapy recommendations [28,40,41,44-52,55,56,59-62,64]. These roles align with EM pharmacy practice surveys in the US and Australia which reported the extent and roles of pharmacists' involvement in trauma or resuscitation care [80]. In another study [50], the pharmacist was trained to be the documenter on the cardiac arrest team, responsible for recording all activities and providing real time quality assurance during the event. This resulted in improved documentation completeness and guideline compliance. Pharmacists facilitated or directly entered medication orders into the electronic medical record during the management of acute haemorrhage [43,56] and during trauma and resuscitation events [55,62]. As collaborative, pharmacist assisted medication charting is an emerging advanced scope role for pharmacists [81,82], this order entry role could be one useful activity to evaluate the impact of new pharmacist services.

During acute stroke management, screening for contraindications to thrombolysis, [41,47,48,52,59,60,64] blood pressure management and monitoring advice [41,47,48,52,60,63,64] were identified as novel pharmacist roles. Two studies reported that the EM pharmacist would assist the emergency physician or neurologist to inform patients and family about the risk and benefits of thrombolysis, and were also involved in medication administration by assisting with supply, bedside preparation and infusion pump programming [52,60]. They also facilitated timely ordering of laboratory tests, antibiotic and fluid bolus ordering and administration within one of the sepsis studies [66]. These pharmacist activities can be considered examples of improving workload efficiencies for other members of the ED resuscitation team.

4.3. Future research

Our systematic review demonstrated that there is a deficiency of large, robust clinical trials on this topic. There was a predominance of cohort studies, most used convenience sampling to determine intervention and control groups and retrospective record review to collect data. This meant that in most cases, patients presenting within hours were in the pharmacist intervention arm and those presenting after hours were controls. This design may lead to selection bias as it has been demonstrated that the altered health care environment and staffing that occurs after hours has an impact on outcomes for critically unwell patients [83,84]. Furthermore, almost all of the studies were cohort studies using a retrospective record review methodology which may be prone to confounding. The influence of a pharmacist presence on clinical benefits such as mortality, LOS and other patient outcomes should be evaluated as part of larger, multicentre trials. Additionally, as 26 of 30 of the included studies were conducted in the US, studies outside the US in countries with similar resources, but differing healthcare systems are needed. Future studies of a pharmacists' benefit in the resuscitation setting should have rigorous, controlled, prospective designs and robust sampling methods to determine intervention and control groups, outcome measures that are confirmed by expert panels, and sample sizes based on power calculations.

4.4. Limitations

Whilst out of our control, publication bias is a possible limitation as it is feasible that studies of pharmacist interventions that were considered unsuccessful might not have been published. We used a comprehensive, but time limited literature search to identify studies relevant to contemporary practice but acknowledge that this may have excluded relevant earlier publications. The main weakness of the review is the variability in study design and methodologic quality of included studies. This heterogeneity in study design and outcomes prevented us from performing a quantitative meta-analysis.

5. Conclusions

The results of this systematic review provide support for a beneficial impact of a pharmacist presence and intervention during resuscitation and medical emergency response team care, with statistically significant improvements in outcomes such as time to initiation of time-critical medications, medication error and appropriateness and guideline compliance. However, studies were predominantly small and retrospective and were not powered to detect differences in patient related measures such as LOS and mortality. Firm conclusions cannot be drawn about the pharmacists' impact on these outcomes. Future research should investigate the clinical impacts of the pharmacist in ED resuscitation settings in controlled, prospective studies with robust sampling methods.

Presentations

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Author contributions

EC, NF and MB conceived the study, designed the protocol, determined the data collection points and validation of the data. EC conducted the literature search, screened and reviewed studies and managed the data. NF and MB screened and reviewed studies and reviewed data items and provided advice on study design and manuscript development. EC drafted the manuscript, and MB and NF contributed substantially to its revision. KI provided expert advice and feedback on the design and review of the manuscript draft. EC takes responsibility for the paper as a whole.

CRediT authorship contribution statement

Elizabeth M. Currey: Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Nazanin Ghahreman-Falconer:** Writing – review & editing, Validation, Supervision, Methodology, Data curation, Conceptualization. **Katherine Z. Isoardi:** Writing – review & editing, Supervision. **Michael Barras:** Writing – review & editing, Validation, Methodology, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no conflict of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2023.10.020.

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