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McCann, J., Jennnings, J.K., Husband, A. et al. (2026) Medication appropriateness and potentially inappropriate medications in older critical care patients: a scoping review. *Drugs & Aging*. ISSN: 1170-229X

<https://doi.org/10.1007/s40266-026-01333-6>

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Medication Appropriateness and Potentially Inappropriate Medications in Older Critical Care Patients: A Scoping Review

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Received: 31 March 2026 / Accepted: 19 August 2026
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Abstract

Background Demand for care of older people in critical care units is increasing. During critical care, new medications are initiated. Assessment of potentially inappropriate medication is not routine within this setting, and the clinical utility of medication appropriateness tools, related interventions and their impact on outcomes in the older critical care population has not yet been reviewed.

Objectives To understand the extent and type of evidence in the assessment of medication appropriateness, intervention strategies and relationship between potentially inappropriate medication use and clinical outcomes in older people in critical care.

Methods The Preferred Reporting of Items for Systematic Reviews and Meta-Analyses extension for scoping reviews was followed. Embase, MEDLINE, CINAHL, APA PsycINFO and Web of Science were systematically searched (April 2025) for studies assessing medication use in critically ill older people (≥ 60 years). Eligible study designs included randomised and non-randomised trials, cohort studies, cross-sectional studies and case-control studies.

Results Ten studies (nine patient cohorts) were included. Most were cohort studies originating from North and South America. Benzodiazepines, opioids and antithrombotics were the most common potentially inappropriate medications reported, identified mostly by Beers Criteria and STOPP Criteria. Critical care length of stay was the most frequently associated clinical outcome. No intervention studies were identified.

Conclusions Medication appropriateness assessment tools have been used to a limited degree to assess medications in older critical care people. Further research is needed to establish their validity, clinical utility and impact on prescribing decisions and to evaluate interventions aimed at improving medication appropriateness and outcomes for older people in critical care.

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Key Points

This is the first scoping review to examine medication appropriateness assessment, interventions and outcomes in older people receiving critical care.

Benzodiazepines, opioids and anti-thrombotics were the most common PIMs identified, and PIM exposure was associated with prolonged critical care stay.

No interventions to reduce PIM exposure in older people in critical care were identified.

Further research is needed to adapt and validate medication appropriateness criteria for critical care settings.

1 Introduction

Critical care units care for some of the most critically ill and vulnerable people in hospitals [1, 2]. The vulnerability of these people is not only influenced by their life-threatening clinical presentations, e.g., organ failure or severe infection, but also by their reliance on advanced organ support technologies (e.g., mechanical ventilation), and acute medication [3]. In older people, these acute medications are commenced in the context of varying degrees of pre-existing multimorbidity, frailty and polypharmacy. Historically, outcome goals of critical care units were ‘based on the premise of saving lives of critically ill patients’ [4]. However, now there is greater recognition of the importance of reducing morbidity and minimising adverse events related to a person’s critical care episode. Research now seeks to improve overall care quality, during and after critical care [5]. The increasing older population in our society, [6] and demand for care in critical care units, [7] requires appropriate use of medication, to deliver effective treatments whilst minimising adverse drug events. Increasing medication appropriateness in the older person in critical care presents an opportunity to improve overall care and outcomes [8].

Clinicians in critical care areas need to regularly consider the pharmacokinetics and pharmacodynamics of medicines used in people with multi-organ failure and extracorporeal support modalities. However, limited geriatric-specific medication training among intensivists poses challenges to achieving optimal care for older people [9]. There is therefore limited awareness of potentially inappropriate medication (PIMs) in older people in critical care units and how PIM use may adversely affect critical care and longer-term outcomes. Currently, medicines optimisation tools used in critical care areas such as medicines reconciliation, medication review, therapeutic drug monitoring and adverse event monitoring may not specifically consider the older person’s unique vulnerability. Medication appropriateness assessment tools, such as the Beers criteria and Screening Tool of Older Persons’ Potentially Inappropriate Prescriptions (STOPP) criteria, are commonly used in the care of older people, identifying PIMs, guiding medication reviews and care plans [10, 11]. However, these tools were not specifically designed or validated for critical care settings [12, 13] so there is uncertainty surrounding the transferability and applicability of these tools in the context of the older person’s critical illness. The European Society of Intensive Care Medicine (ESICM) strongly recommends for a medication review to be undertaken prior to or as soon as possible following transfer from critical care [14], but it is unclear whether medication appropriateness assessments have a role in medication reviews conducted routinely during an older person’s critical care episode [15]. As existing medication

appropriateness tools have not been systematically assessed for their utility within the complexity of the older person in critical care, a scoping review is needed to describe tools studied, identify limitations in clinical utility and inform future medication appropriateness research in this unique population. The aim of this scoping review is to describe how medication appropriateness is assessed for older critical care patients (≥ 60 years), what intervention strategies are used to minimise PIM prescribing and what is the relationship with clinical outcomes.

2 Methods

2.1 Protocol and Registration

The scoping review protocol was pre-registered with Open Science Framework (OSF, osf.io/3cpf7). The Preferred Reporting of Items for Systematic Reviews and Meta-Analyses-extension for scoping reviews (PRISMA-ScR) framework was used for the review and report [16] (Supplementary Material 1).

2.2 Eligibility Criteria

Studies had to include older people (≥ 60 years of age) admitted to any critical care (intensive care or high dependency unit) setting. Studies must also have used either; (1) a method or tool for assessing medication appropriateness, or (2) a specific medicine and/or its class that has been pre-determined as potentially inappropriate. To meet the aims of the review, studies were required to evaluate clinical outcomes associated with PIM use in critical care. An ‘older person’ was defined in this review as being aged 60 or over, in accordance with World Health Organization’s (WHO) definition of older people in developing countries [17].

Types of studies that would clearly address the aims of the review and therefore eligible for inclusion were randomised and non-randomised trials, prospective and retrospective cohort studies, cross-sectional studies and case-control studies. Eligible studies were not limited by year of publication, language of publication or geographical location to ensure a comprehensive and unbiased overview of the evidence.

2.3 Information Sources and Search Strategy

A pilot search of Embase and MEDLINE was conducted to identify relevant studies and articles on the topic. To ensure the review question had not been addressed in any published or ‘in-process’ reviews, an online search of OSF and PROSPERO databases was undertaken prior to conducting the review. The text words contained within the titles and abstracts of relevant articles and the index terms used to

describe articles were used to develop a full search strategy for Embase (Ovid), MEDLINE (Ovid), CINAHL (EBSCO), APA PsycINFO and Web of Science (Supplementary Material 2). A medical librarian was consulted to help design the most appropriate search strategy. The search strategy, including all identified keywords and index terms, were adapted for each individual database and/or information source and databases were searched from 1946 to 2025.

2.4 Selection of Sources of Evidence

Following the search, all identified citations were collated and uploaded into Covidence (*Veritas Health Innovation, Australia, 2024*) and duplicates were removed. Title and abstract screening followed by full-text screening was undertaken by two reviewers independently [anonymised for peer review]. Any disagreements between the reviewers at each stage of the screening process were resolved through discussion and if consensus could not be reached, arbitration was sought from another member of the research team [anonymised for peer review]. The Cohen's κ statistic was used to test interrater reliability. Forward and backward citation searching of included studies was undertaken to identify additional studies which may be eligible for inclusion within the review.

2.5 Charting the Data

A data extraction tool was designed (Supplementary Material 3) to ensure reviewers systematically captured the information needed to address the review objectives. Data extraction was completed by [anonymised for peer review] and independently validated by [anonymised for peer review] [18].

2.6 Collating, Summarising and Synthesis of Results

Findings were collated in a summary of findings table and narratively synthesised according to the scoping review objectives.

2.7 Classification of PIMs

The top five PIMs identified within each study were collected, after which the common PIMs across all studies were pooled and reported. A limit of five PIMs was chosen because frequencies tended to drop sharply beyond the fifth medication and PIMs identified once by one study tended not to appear in others, resulting in high PIM heterogeneity. Exceptions were studies that did not report their full list of PIMs [19] or if there were fewer than five PIMs included in the study [20]. PIMs were classified using the Anatomical Therapeutic Chemical (ATC) classification system [21]. The name and corresponding ATC code were reported. When

feasible, PIMs were classified at the Chemical Subgroup (fourth level) of ATC classification.

3 Results

Ten papers were included, but two studies [22, 23] used different medication appropriateness criteria with the same patient cohort and were hence referred to as a single study for the purposes of the review. The PRISMA flowchart is displayed in Fig. 1. Covidence generated Cohen's κ statistic was acceptable (0.53) at the full-text screening stage [24]. All studies were undertaken in intensive care units (ICUs), and this term is used throughout to specify this type of critical care unit. The full summary of findings can be found in Table 1.

3.1 Characteristics of Included Studies

Studies originated from five countries, three from the USA [19, 20, 25] and three from Brazil [26–28] and the remainder from Turkey ($n = 2$), [22, 23] Egypt ($n = 1$), [29] and China ($n = 1$), [30] (Table 1). All studies were published in English. Publications covered the period 2009 to 2025, with six being published after 2020 [22, 23, 26, 28–30]. The study designs consisted of cross-sectional studies ($n = 4$) [22, 23, 27, 30], retrospective cohort studies ($n = 5$) [19, 25, 26, 28, 29] and one prospective cohort studies [20]. Patient cohort sizes ranged from approximately 40–600 patients with most including more than 150 patients [20, 25, 27, 28, 30]. Five studies included patients ≥ 60 years [20, 25, 27–30], and four studies included patients aged ≥ 65 years [19, 22, 23, 30]. Mean age of patients ranged from 66.8 to 76.7 years [20, 22, 23, 26].

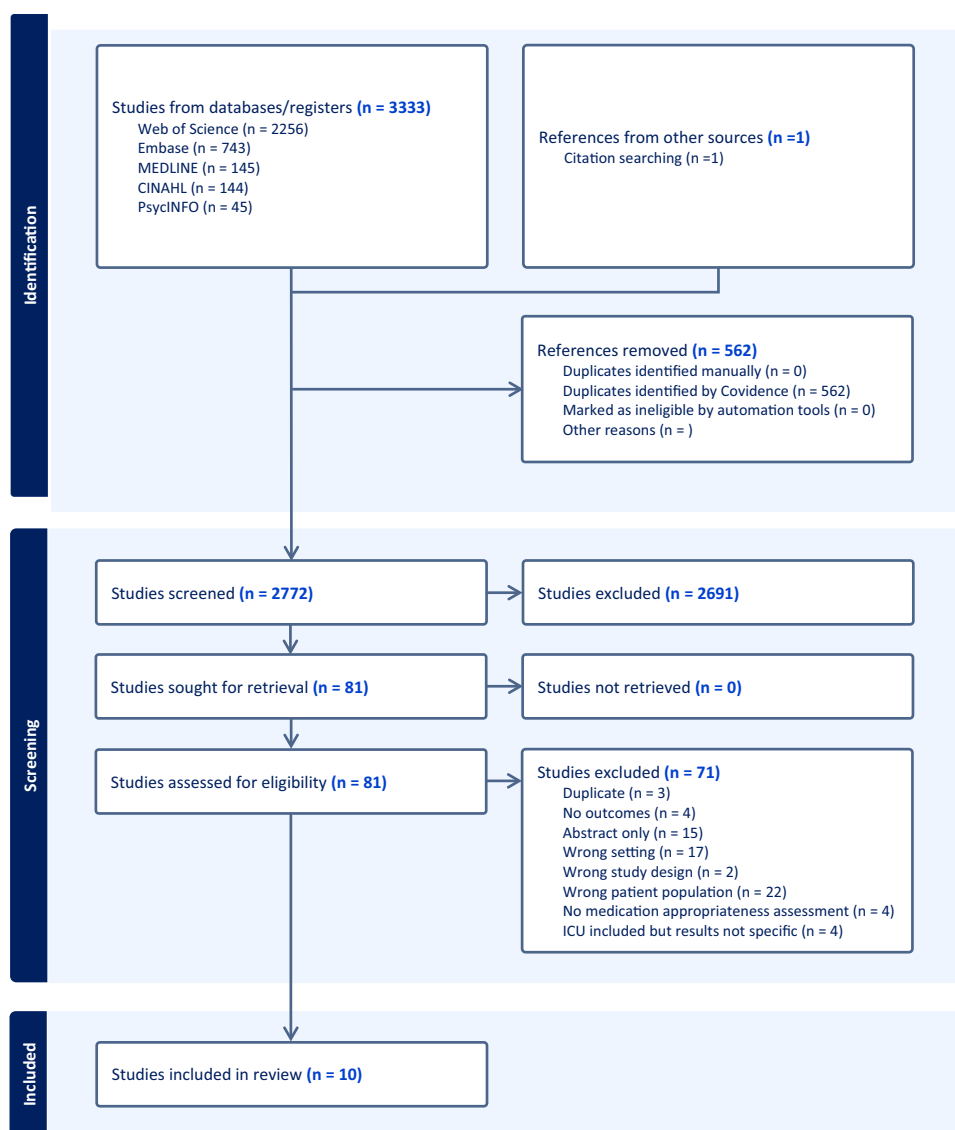
3.2 Medication Appropriateness Assessment

The Beers criteria was the most common medication appropriateness tool to identify PIMs in ICU studies (7, 78%) [19, 22, 25–28, 30]. Six studies (67%) used the STOPP criteria [19, 22, 25, 26, 29, 30] and one study each used the EU(7)-PIM list [22], the Chinese criteria [30] and the TIME-to-STOP criteria [23]. Two studies used the Anticholinergic Cognitive Burden (ACB) calculator to estimate the cumulative exposure to anticholinergic medications [26, 29]. One study calculated patients' daily Drug Burden Index (DBI) [19]. One study used Micromedex [27] and two used UpToDate [26, 27] to identify PIMs via drug–drug interactions.

3.3 Common PIMs Identified

The most common PIMs reported were hypnotics and benzodiazepine derivatives and opioids (each $n = 7$), followed

Fig. 1 PRISMA flowchart for the searching and screening of studies for review



closely by antithrombotic agents ($n = 6$). Other PIMs identified were antipsychotics, propulsives, anticholinergics and anti-arrhythmics class III (each $n = 4$). The top five PIMs reported across the studies are presented in Fig. 2.

3.4 Outcomes

Six clinical outcomes associated with PIM use in critical care were reported by the studies. These included ICU length of stay (LoS) ($n = 6$) hospital LoS ($n = 4$), mortality ($n = 4$), adverse drug reactions (ADRs) and drug–drug interactions ($n = 3$), ICU delirium ($n = 2$) and readmission ($n = 1$). The clinical outcomes reported by each study are in Table 2.

Table 1 Summary of findings from included studies within the review

Study details	Study design	Size (<i>n</i>)	Patient age	Type of ICU	Timing of PIM assessment and assessor	PIM criteria	Most common PIMs	Key outcome findings
Aydemir et al. 2021 [22] And Oncu et al. 2023 [23] Turkey	Cross-sectional study	139	(≥ 65 years) 65–74: 46.8%, 75–84: 36%, 85+: 17.3%	Medical, surgical	No data	2019 Beers, STOPP v2, EU(7)-PIM and TIME-to-STOP	Combined midazolam and fentanyl (58.3%), enoxaparin (29.5%), propulsives—metoclopramide (25.2%), Amiodarone—antiarrhythmics (23.7%), antipsychotics—Haloperidol (15.8%)	2019 Beers identified most PIMs (<i>n</i> = 80.6%) Only PIMs from the 2019 Beers criteria were associated with longer mean ICU LoS (<i>p</i> = 0.028)
Pisani et al. (2009). USA [20]	Cohort study (prospective)	304	Mean age: 75 years (≥ 60 years)	Medical	Daily during ICU Nurses	Clinician expertise	3 medicine combination: BZDs, opioid and propofol (22%), BZDs and opioid (19%), 4 drug combination: BZD, opioid, propofol and haloperidol (17%)	BZD or opioid use increased ICU delirium (RR 1.64; 95% CI 1.27–2.10, <i>p</i> < 0.001) In non-dementia, BZD/opioid use doubled delirium duration (RR 2.43; 95% CI 1.65–3.55, <i>p</i> < 0.001)
Floroff et al. (2014). USA [19]	Cohort study (retrospective)	112	65–74: 36.6%, 75–84: 36.6%, 85+: 26.8% (≥ 65 years)	Neuroscience	Daily Not mentioned	2012 Beers and STOPP	Barbiturates (23%) Opioids (18%) H2RA	> 2 PIMs increased hospital stay 4 days longer than ≤ 2 PIMs (<i>p</i> < 0.001) After adjusting APACHE II and CCI, ≤ 2PIMs had shorter ICU and hospital stays by 2.16 and 4.5 days, respectively (both <i>p</i> < 0.001)
Rahman et al. (2019). USA [25]	Cohort study (retrospective)	346	65–74: 51.7%, 75+: 48.3% (≥ 65 years)	Medical	At ICU admission and discharge Two researchers	2012 Beers, 2015 Beers and STOPP	BZD (24.6%) Opioids (22.5%) Loop diuretics (15%) Skeletal muscle relaxants (11.6%) Antiarrhythmics and Salicylates (both 11.3%)	Beers identified significantly more PIMs than STOPP No differences in hospital or ICU re-admission or mortality outcomes were found when comparing Beers versus STOPP PIMs STOPP-PIMs were associated with longer ICU stays (RR 1.24; 95% CI 1.11–1.38; <i>p</i> < 0.001) and hospital stays (RR 1.24; 95% CI 1.16–1.33; <i>p</i> < 0.001) than Beers
Carizio et al. (2025). Brazil [26]	Cohort study (retrospective)	41	Mean age: 66.8 years (≥ 60 years)	Unspecified	Daily during ICU Pharmacist	2019 Beers, STOPP, Micromedex Solutions, Drug Interaction Checker and ACB calculator	Omeprazole (29.6%), Insulin (rapid-acting) (28.8%), Multiple drugs with anticholinergic effects (25.6%), Duplicate drug class (22.6%), Opioid without a laxative (19%) <i>Drug-drug interacting PIMs</i> Fentanyl X Midazolam (4.9%), Bromopride X Fentanyl (3.6%), Meropenem X Tramadol (3.0%), Bromopride X Midazolam and Bromopride X Tramadol (2.8%), Fentanyl X Midazolam (2.7%)	<i>Suspected ADRs</i> Thrombocytopenia (3) (micafungin, lamotrigine and linezolid). Sedation and lethargy (3) (risperidone, lorazepam, quetiapine hemifumarate). Nausea and vomiting (3) (tramadol, methadone and micafungin). Leukopenia (2) (lamotrigine and linezolid). GI bleed (1) (heparin). Diarrhoea (1) (meropenem). Hypokalaemia (1) (furosemide)

Table 1 (continued)

Study details	Study design	Size (n)	Patient age	Type of ICU	Timing of PIM assessment and assessor	PIM criteria	Most common PIMs	Key outcome findings
Galli et al. (2016). Brazil [27]	Cross-sectional study	599	Median (IQR) age: 71 (65–77) 60–74: 65.6%, 75–84: 27.7%, 85+: 4.7% (≥ 60 years)	Medical and Cardiovascular	(1) Before admission, (2) during ICU, (3) discharge from ICU and (4) hospital discharge Pharmacist/s	2012 Beers, Micro-medex Solutions and UpToDate	Metoclopramide (28.6%), Vasodilators (13.2%), BZD (8.4%), Antipsychotics (first and second generation) (8.3%), Antiarrhythmic drugs—amiodarone (7.8%)	24.8% (N = 1864) of PIMs were started in the ICU, 10.9% were continued post-ICU and 3.9% were prescribed at discharge ICU LoS (R = 0.384, $p < 0.001$), hospital LoS (R = 0.313, $p < 0.001$) and delirium and (R = 0.215, $p < 0.05$) were associated with PIM count 46.9% of ADRs were attributed to PIMs, and included: five upper GI bleed NSAIDs), four falls with fractures/depressed mental status (BZDs), four cardiac arrhythmias/visual disturbances due to digoxin poisoning (digoxin > 0.125 mg/day)
Sichieri et al. (2024). Brazil [28]	Cohort study (retrospective)	314	60–74: 67.5%, 75+: 32.5% (≥ 60 years)	Medical, Surgical and Speciality	Not mentioned Nurses and Pharmacists	2019 Beers	Metoclopramide (95.8%), Insulin (92.4%), Antipsychotics (66.7%), NSAIDs (54.1%), BZDs (52.1%) <i>Drug-drug interacting PIMs</i> Antipsychotics $X \geq 2$ other CNS-active drugs (66.7%), BZD and non-BZD, BZD-receptor agonist hypnotics $X \geq 2$ other CNS-active drugs (43.1%), Opioid receptor agonist analgesics $X \geq 2$ other CNS-active drugs (34.7%), Antidepressants $X \geq 2$ other CNS-active drugs (24.3%), Anticholinergics X anticholinergics (22.2%)	ICU LoS and number DDIs increase with PIM use Each additional hospital day increased the odds of PIM prescription by 7.4% (OR = 1.074, 95% CI = 1.020–1.131, $p = 0.007$) Each additional ICU medication increased the odds of receiving a PIM by 17.3% (OR 1.173, 95% CI 1.059–1.299, $p = 0.002$) Patients with ≥ 10 DDI had 2.43 times higher odds of receiving a PIM r (OR = 2.430, 95% CI = 1.189–4.965, $p = 0.015$)
Elsorady et al. (2022). Egypt [29]	Cohort study (retrospective)	152	Mean (SD) by mortality status at hospital discharge <i>Alive</i> : 72.2 (+/– 7.8) <i>Dead</i> : 76.9 (+/– 8.5) (≥ 60 years)	General	Not mentioned	STOPP version 2 and ACB calculator	Anticholinergics (53.9%), Opioids (13.8%), Drugs causing constipation in PTs with chronic constipation (9.9%), Aspirin plus clopidogrel (8.6%), Antiplatelets, with anticoagulant, (5.9%), aldosterone antagonist with ACEi (5.9%) <i>Common Drugs with Anticholinergic Properties</i> : Ipratropium (44.1%), Furosemide (32.2%), Steroids (22.4%), Piperacillin (21.7%), Fentanyl (13.2%)	PIM use in ICU increased in-hospital mortality over 5-fold ($p < 0.001$), with each additional PIM doubling the odds of death ($p < 0.001$) ICU anticholinergic use increased in-hospital mortality 2.5-fold ($p = 0.024$), with each additional drug nearly doubling the odds ($p < 0.001$)

Table 1 (continued)

Study details	Study design	Size (n)	Patient age	Type of ICU	Timing of PIM assessment and assessor	PIM criteria	Most common PIMs	Key outcome findings
Bai et al. (2022), China [30]	Cross-sectional study	369	65–74: 50.4%, 75–84: 39.8%, 85+: 9.8% (≥ 65 years)	Cardiac	At ICU admission and discharge Pharmacist and Doctor	2019 Beers, STOPP version 2 and Chinese criteria	<i>At critical care admission:</i> Clopidogrel (50.7%), Diuretics (32.2%), BZDs (14.1%), Antispasmodics—atropine (11.1%), Theophylline (6.8%) <i>At critical care discharge:</i> Clopidogrel (46.3%), Diuretics (36.9%), Dabigatran/Rivaroxaban (6.2%), Theophylline (6.0%), BZD (5.7%)	Poor consistency and agreement between the three criteria Each additional medication at ICU admission increased PIM risk by 15–26% (all $p < 0.001$) Longer ICU stay increased the odds of PIMs at discharge (Beers 2019: OR 1.120; $p = 0.036$)

Key: LoS, length of stay; IQR, inter-quartile range; ICU, intensive care unit; Beers, Beers criteria; STOPP, Screening Tool for Older Persons' Prescriptions; BZD, benzodiazepines; RR, rate ratio, p , p -value/probability value; PIM, potentially inappropriate medication; 95% CI, 95% confidence interval; H2RA, histamine 2 receptor antagonist; APACHE II, acute physiology and chronic health evaluation II; CCI, Charlson Comorbidity Index; R, correlation coefficient; GI, gastrointestinal; NSAIDs, non-steroidal anti-inflammatory drugs; CNS, central nervous system; OR, odds ratio; ACEi, angiotensin converting enzyme inhibitor

3.4.1 ICU Length of Stay

Six studies found a positive association between the use of PIMs (primarily identified using the Beers criteria) and the ICU Length of Stay (LoS). A cohort study looking at PIM use in neuroscience ICUs [19], found that exposure to more than two PIMs in ICU was associated with an increased median ICU LoS by approximately 2 days compared with those taking two or fewer PIMs, after adjusting for Acute Physiological and Chronic Health Evaluation II (APACHE II) (a severity of illness score to predict mortality within the ICU) [31] and Charlson Comorbidity Index (CCI) (a score to predict long-term mortality based on the impact of multiple concurrent health conditions) [32]. Sichieri et al. found that in their cohort of older patients who were exposed to a PIM during ICU, mean LoS was twice as long as those who did not receive a PIM [28]. A 2022 cohort study ($n = 369$) in a cardiac ICU comparing the use of the 2019 Beers criteria, STOPP criteria and Chinese criteria, found that only PIMs identified by the Beers criteria were significantly associated with ICU LoS [30]. Similarly, the ICU LoS was only significantly associated ($p < 0.05$) with Beers criteria PIMs by another cohort study ($n = 139$) that included three different criteria [22]. Contrastingly, Rahman et al., compared the use of PIMs identified by three different criteria [25] and found that PIMs identified by the 2012 Beers criteria was associated with shorter ICU LoS than those identified by STOPP criteria. However, there was no comparison between the pooled use of PIMs identified from any criteria and patients who did not receive PIMs in this study.

3.4.2 Hospital Length of Stay

Similarly to ICU LoS, four studies found positive association between PIM use in ICU and overall hospital LoS. The study based in neuroscience ICU found that patients who received > two PIMs were hospitalised for more than 4 days longer than those who received ≤ two PIMs [19]. Another cohort study demonstrated a weak positive association between hospital LoS and number of PIMs ($r = 0.313$) [27]. Sichieri et al. examined the factors that predicted PIM use and found that for each additional day in hospital, the odds of being prescribed a PIM increased by 7.4% [28]. Consistent with the ICU LoS outcome, the cohort study by Rahman et al., found that PIMs from the STOPP criteria had a longer hospital LoS, than Beers criteria PIMs [25].

3.4.3 Mortality

Studies defined mortality as either in-hospital mortality (death occurring at any point during hospitalisation), or as 28-day mortality (death within 28 days of ICU admission). A general ICU cohort study [29] using the STOPP criteria

Fig. 2 Heatmap showing the common potentially inappropriate medications reported within the studies



found that the use of a PIM in ICU was associated with increased odds of in-hospital mortality by over five times compared with no PIM exposure and each additional PIM doubled the odds of mortality. The use of anticholinergic medications was associated with more than double (2.5) the odds of in-hospital mortality compared with non-exposure [29]. A cross-sectional study assessing the occurrence of ADRs in ICU reported that of the 23 ADRs attributable to the use of PIMs, five patients experienced reactions resulting in death during ICU stay [27]. However, the remaining studies assessing in-hospital mortality or 28-day mortality demonstrated either no association [25] or no significant difference in 28-day mortality in those receiving a PIM compared to those that did not [22, 23].

3.4.4 Adverse Drug Reactions and Drug-Drug Interactions

Across the two studies assessing ADRs, there were a total of 34 reported ADRs [26, 27]. The most common type of ADR was gastrointestinal bleed (6, 37.5%) with the likely causal drugs reported as nonsteroidal anti-inflammatory drugs (NSAIDs) and heparin. Sedation, lethargy or confusion was recorded four times (25%) and the likely causal PIMs were reported as antipsychotics, lorazepam and dexchlorpheniramine. Other ADRs include cardiac arrhythmias (4, 25%) and visual disturbances due to digoxin toxicity and nausea and vomiting (3, 19%).

Ten drug–drug interactions (DDIs) were reported across the two studies assessing DDIs [26, 28]. Common interacting drugs included opioids (6, 60%), benzodiazepines (4, 40%) and anticholinergics (2, 20%), again likely to contribute to central nervous system suppression and confusion.

3.4.5 Delirium

A cohort study assessing the impact of benzodiazepine and opioid use on the duration of delirium in critical care [20] found that the use of these medicines showed a strong association with duration of delirium. In the patient subgroup without dementia, there was a significant increase in the rate of delirium in those who received a benzodiazepine or opioid [20]. Similarly, the use of haloperidol in ICU showed a positive association with the duration of ICU delirium [20], although it was not possible to ascertain whether haloperidol use was in response to delirium symptoms. Comparably, Galli et al. found that as the number of PIMs increased, the number of days of delirium increased [27].

3.4.6 Re-admission

The single study that assessed the relationship between PIMs and ICU and hospital re-admission reported that there were no differences between critical care and hospital re-admission rates between PIMs identified by the 2012 Beers, 2015 Beers and STOPP criteria [25].

4 Discussion

We found that studies of medication appropriateness in older people in critical care comprised primarily of small retrospective cohort studies conducted in medical ICUs in North and South America. We identified no intervention studies. Beers and STOPP Criteria were the most common medication appropriateness assessment methods used, and PIMs were mostly assessed daily in ICU by pharmacists.

Benzodiazepines, opioids and anti-thrombotic agents were the most identified PIMs. Increased ICU LoS was the most common outcome associated with PIM exposure.

Older people in critical care are exposed to high numbers of high-risk medication. Despite this, current ESICM consensus-based recommendations for care of the very old person in ICU provide a weak recommendation for medication review in intensive care and a strong recommendation after ICU [14]. Contrastingly, recent guidance from the Society of Critical Care Medicine (SCCM) in the USA, made no recommendation for a specialised post-ICU follow-up for older people after a critical illness due to the uncertain evidence and heterogeneity in post-ICU follow-up interventions [33]. However, other acute care guidance recommend a medication review on hospital admission, inpatient and hospital discharge in those on multiple medicines [34]. Studies by Morandi et al. [35, 36], stress the importance of evaluating medication appropriateness at multiple time points; pre-admission, pre-critical care ward, during critical care discharge and post-critical care to detect when PIMs were initiated during a person's critical care episode, on account that prescribing practices change across levels of hospital care [37]. They found that most PIMs were started during critical care stay and emphasised the need for better systematic coordination across care transitions and implementation of interventions within critical care [35, 36].

The Beers Criteria and STOPP Criteria were the most frequently used medication appropriateness assessment tools, yet there are several key differences in terms of their structure, number of indicators and clinical utility. The Beers Criteria, developed by the American Geriatrics Society, contains 139 individual PIM indicators organised by medication or medicine class [10]. The STOPP criteria is a European-based criteria containing 80 PIM criteria, organised by physiological system [11]. As the STOPP Criteria defines PIMs according to more complex context-based considerations, it is often considered more clinically relevant than the Beers Criteria [38, 39]. A previous study comparing the Beers and STOPP criteria reported a kappa value of 0.093 [40], indicating poor agreement. Therefore, the medications classified as PIMs by each criterion are not consistently identified.

The most commonly identified PIM classes, benzodiazepines, opioids and anti-thrombotics are high-risk medicines in critical care patients [41]. Benzodiazepines, identified through the STOPP v2 criteria, was the most common PIM-class (22.1%, $n = 16,687$ admissions) recorded within a large-scale Europe-based longitudinal study of hospitalised older patients [42]. In critical care, international guidelines on pain, agitation, delirium and sleep recommend minimising benzodiazepine sedation, when possible, in preference to propofol or dexmedetomidine [43], with the result being reduced benzodiazepine use in older people during their intensive care stay [44, 45]. There is also evidence that

Table 2 Clinical outcomes associated with PIM use

	ICU Length of Stay	Hospital Length of Stay	Mortality	ADR and/or DDIs	Delirium	ICU and Hospital Re-admission
Carizio et al. [26]				☑		
Bai et al. [30]	☑	☑				
Aydemir et al. and Oncu et al. [22, 23]	☑		☑			
Elsorady et al. [29]			☑			
Floroff et al. [19]	☑	☑	☑			
Galli et al. [27]	☑	☑	☑	☑		
Pisani et al. [20]					☑	
Rahman et al. [25]	☑	☑	☑		☑	☑
Sichieri et al. [28]	☑			☑		
Key: ☑= associated outcome reported; ICU= intensive care unit; ADR= adverse drug reaction; DDI= drug-drug interaction						

post-critical care exposure to benzodiazepines in older people is being restricted within healthcare systems [46, 47]. Additionally, despite US SCCM guidance recommending not to use antipsychotic medication for the prevention of, and no recommendation on use in the treatment of delirium in older people with critical illness [33], antipsychotics, such as haloperidol and quetiapine, were common PIMs identified in this review. Nevertheless, antipsychotics are still commonly used in the treatment of hyperactive delirium in people in critical care [48, 49]. This highlights the considerable clinical complexity involved, with delirium arising from multiple potential precipitants, including PIM exposure, while antipsychotics may be used as a risk mitigation strategy to avoid the use of other potentially more deleterious PIMs, such as benzodiazepines.

Opioids are a well-established PIM-class in older patients [50], with a large retrospective Canadian cohort study showing they were commonly identified at PIMs at hospital admission and discharge from the Beers and STOPP criteria [51]. Whilst practice guidelines encourage use of multimodal and non-opioid analgesics [43], only a minority of critical care units internationally have guidelines to support opioid and sedative weaning with low implementation [52]. In Sweden, older age was a risk factor for chronic opioid use after a critical care admission and is associated with an increased mortality at 6–18 months post-admission [53]. In contrast, a Canadian cohort study in critical care patients (median age 64 years), reported older people (> 75 years) with more comorbidities were less likely to continue an opioid prescription on hospital discharge [54].

Antithrombotic medication (outside of venous thromboembolism prophylaxis) is less common than benzodiazepine and opioid use in critical care patients [55]. Older people are more likely than younger people to be admitted to a critical care unit on antithrombotic medicines. In turn, such pre-exposure is associated with worse outcomes, e.g., after traumatic brain injury [56]. It is common practice for pre-existing anticoagulants and non-aspirin antiplatelets to be omitted during a person's critical illness unless benefits outweigh the risks. Moreover, there are higher clinical thresholds to commencing anticoagulants for atrial fibrillation in the critically ill person [57, 58].

Although no intervention studies were found in our review, there are studies evaluating and proposing medication-related interventions to reduce inappropriate prescribing in older people in non-critical care contexts. In a literature review, Marra et al. [59] identified potential interventions to reduce inappropriate medication exposure in older people in critical care using appropriateness criteria, medication reviews and multiprofessional teams (geriatrician and/or clinical pharmacist). A Canadian community-based clinical trial used a pharmacist-led intervention consisting of educating the patient on why their medication is considered

a PIM and sending the prescribing physician an evidence-based pharmaceutical opinion [60]. They found that compared with the control group of usual care, 42.7% of patients ($n = 248$) were deprescribed their PIM compared with control group (12.0%, $n = 241$), at 6 months [60]. Critical care units are unique clinical settings with highly heterogeneous patient groups, which makes developing and implementing standardised medication-focused intervention approaches challenging. A 2015 review [61] explains that the pharmacokinetic and pharmacodynamic changes that occur during critical illness, e.g., effects of organ support, mean that medicines management strategies, such as medicines optimisation, i.e., a person-centred approach to guide safe and effective medicines use [62], differ from those used in less acute settings. The rapidly changing physiology and often complex polypharmacy seen in critically ill patients often requires more individualised and adaptive approaches for medicines management [61], and recovery from critical illness can leave patients frailer, increasing their vulnerability to insults such as PIMs [63].

Clinical outcomes, such as length of stay and mortality, are common outcomes associated with PIM use in older adults. In a retrospective cohort study of hospital patients ≥ 65 years, an increased number of PIMs was associated with a significantly greater chance of prolonged hospital stay (odds ratio = 3.47) and increased in-hospital mortality (odds ratio = 2.68) compared with patients who were not exposed to an increase in PIMs [64]. It is important to note that the association PIM use and LoS may be bidirectional. While PIM exposure may contribute to prolonged hospitalisation from adverse drug event outcomes, an increased LoS may also lead to greater PIM burden among older people in hospital settings [65, 66].

In a recent systematic review and meta-analysis, PIM exposure in older people was reported to be associated with a significantly higher risk of rehospitalisation within 3 months (OR 1.47 [95% CI 1.02 to 2.13], $p = 0.045$), albeit with very low strength of evidence [67]. Outcomes such as adverse drug reactions and DDIs as well as delirium, were not frequently reported by the studies in our review. However, in a systematic review by Leong et al. [68], opioids (fentanyl and morphine) use in critical care adults was associated with a doubling of delirium occurrence. In addition to the clinical outcomes reported within this review, US SCCM guidance highlights the priority for future research to focus on patient-centred outcomes, such as short- and long-term functional and cognitive outcomes, maintaining community independence and mobility, when designing and evaluating geriatric-specific models of ICU care [33].

This scoping review provides the first broad exploration of medication appropriateness in older people in critical care from diverse economic healthcare systems. It has several strengths: pre-registered and protocolised, followed a

rigorous and systematic methodology to ascertain transparency, reliability and reproducibility. Independent screening and data extraction by two reviewers minimised selection bias and supported data validity. Potential limitations include heterogeneity in study classification of PIMs (medication class versus medication) affecting the level of ATC coding we could employ [21]. The majority of the studies included in the review were conducted across North and South America, with no studies originating from Western Europe limiting generalisability. Studies varied in how they applied clinical context within the Beers [10], and STOPP criteria [11], leading to the potential for over-reporting PIMs. Additionally, as it was not clear how studies applied clinical context for defining PIMs, some medications classified as PIMs may have been deemed clinically appropriate in specific critical care situations, such as keeping the person comfortable during mechanical ventilation. Finally, not all studies controlled for potential baseline confounders limiting the strength of association between PIMs and clinical outcomes.

Although established criteria, such as the Beers, STOPP, EU (7)-PIM etc., can identify medicines as PIMs, these criteria were not specifically designed or validated for use in critical care. Not all medicines routinely prescribed in critical care settings are included in these criteria (e.g., propofol); neither do they include specific clinical context (e.g., mechanical ventilation) leading to challenges with appropriate prescribing assessment. Further research is needed to determine the utility of these medication appropriateness criteria, clinical pathway timing and adaptations required for use in context of critical care. Correction for potential confounders to clinical outcomes are also needed to confirm relationships. Finally, implementing medication appropriateness reviews and evaluating the impact of related interventions on care outcomes for the older person in critical care are still required.

5 Conclusions

Studies utilising medication appropriateness tools in older people in critical care identify common PIM exposure and these are often associated with adverse clinical outcomes. No intervention studies related to medication appropriateness tool use were identified. Further research is needed to determine their validity, clinical utility and timing of these medication appropriateness criteria, and impact on prescribing decisions in the context of care of older people in critical care.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40266-026-01333-6>.

Funding This research is funded by the National Institute for Health and Care Research (NIHR) Newcastle and Greater Manchester Patient Safety Research Collaborations (PSRCs) [NIHR204291] [NIHR204295]. RSB is supported by a National Institute for Health and Care Research (NIHR) Senior Clinical and Practitioner Research Award [NIHR304524]. The views expressed are those of the authors and not necessarily those of the NHS, the National Institute for Health and Care Research or the Department of Health and Social Care.

Declarations

Conflict of Interest The authors have no competing interests to declare that are relevant to the content of this study.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent to Publish All authors consent to publication of the research material.

Availability of Data and Materials This scoping review does not involve generation of new data. All information discussed is drawn from previously published sources.

Code Availability Not applicable.

Author Contributions Jessica McCann led on the literature search, data extraction and writing of the manuscript. Jen K. Jennings supported the literature search and data extraction as a second reviewer. Richard S. Bourne, Andy Husband and Darren M. Ascroft contributed to the conceptualisation of the review, data interpretation and review of the final manuscript. All authors have read and approved the final submitted manuscript, and agree to be accountable for the work, if required.

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