Drugs & Aging (2022) 39:333–353
https://doi.org/10.1007/s40266-022-00940-3

REVIEW ARTICLE

Scoping Review of Studies Evaluating Frailty and Its Association with Medication Harm

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Accepted: 2 May 2022 / Published online: 22 May 2022

Abstract

Introduction Frailty is associated with an increased risk of death and morbid events. Frail individuals are known to have multiple comorbidities which are often associated with polypharmacy. Whilst a relationship between polypharmacy and frailty has been demonstrated, it is not clear if there is an independent relationship between frailty and medication harm.

Aims This scoping review aimed to identify and critically appraise studies evaluating medication harm in patients with frailty.

Methods PubMed, EMBASE, CINAHL and Cochrane databases were searched from inception until 1 February 2021 using key search terms that are synonymous with frailty (such as frail and frail elderly) and medication harm (such as adverse drug events and adverse drug reactions). To be included, studies must have identified medication harm as a primary or secondary outcome measure, and used a frailty assessment tool to determine frailty, or clearly defined how frailty was assessed. Data were narratively synthesised and presented in tables. The checklist from the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies from the National Heart, Lung, and Blood Institute was used to assess the quality and risk of bias of studies that met the inclusion criteria.

Results Of 2685 retrieved abstracts, 24 underwent full-text review and nine studies met the inclusion criteria. Three studies were retrospective cohort studies, and six were prospective observational studies. Six studies comprised two distinct groups of frail and non-frail individuals, and the remaining three studies evaluated medication harm in an entirely frail population. Seven studies used validated frailty tools such as the Clinical Frailty Scale, Fried Frailty Index, and Fried Frailty Phenotype. Two studies measured frailty using self-defined criteria. Overall, frail individuals were at risk of medication harm with rates ranging between 18.7 and 77% across the nine studies. However, whether frailty is an independent predictor of medication harm remains uncertain, as this was only evaluated in one study. The risk of bias assessment identified limitations in methods and reporting with all nine studies.

Conclusion This scoping review identified nine studies evaluating medication harm in frail patients. However, all were limited by the methodological quality and inadequate reporting of study factors. There are few high-quality studies that described a relationship between medication harm and frailty. More robust studies are required that examine the independent relationship between frailty and medication harm, after adjusting for all possible confounders and in particular polypharmacy.

1 Introduction

Medication harm and frailty have both been associated with adverse outcomes, including hospital admission, increased length of hospital stay, and mortality [1, 2]. Frailty is common in older individuals, affecting 26% of Australian adults aged 65 years and older, with a further 48% identified as pre-frail [3]. Internationally, the prevalence of frailty across all age groups has been reported as up to 14% [3]. Frail individuals often have multiple comorbidities [4]. In frail

Key Points

A variety of different methods are used to detect medication harm and to evaluate causality across studies.

Studies assessing frailty as an independent predictor of medication harm are limited in number and of poor methodological quality.

In general, frail individuals appear to be at high risk of medication harm and should be prioritised for medication review and optimisation.

Frailty may be incorporated within risk prediction tools to help identify patients at high risk of medication harm for a timely and targeted medication review.

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individuals, minor stresses may lead to a disproportionate decline in physical and mental well-being which may not recover to baseline [5]. The deficit accumulation model of frailty [6] shows that individuals with multiple health deficits are at increased risk for adverse outcomes such as falls, hospitalisation, and mortality [7, 8].

Fried et al. describe frailty as a clinical syndrome in which three or more of the following criteria are present: unintentional weight loss (10 pounds in the past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity. Rockwood et al. have defined frailty as deficit accumulation from the loss of functional reserves (energy, physical ability, cognition, health). Whilst old age is not synonymous with frailty, frailty syndromes are more common in older adults [9], with studies reporting up to 59% of older adults living in the community as being frail [10]. Given that frailty is associated with multiple adverse patient outcomes, a patient's level of frailty should be considered in therapeutic decisions, particularly for older adults who are also often subject to polypharmacy, and who may be at an increased risk of medication harm [11]. Other potential factors include inappropriate prescribing and pharmacokinetic/pharmacodynamic changes associated with aging which may put individuals with frailty at risk of poorer patient outcomes [11].

Medication harm is an area of growing interest with clinicians and researchers who seek interventions to improve patient safety [12]. Medication harm is defined as "any negative patient outcome or injury, related to medication use, irrespective of severity or preventability" [13]. It is especially common in older adults [14], may result in hospitalisation, morbidity, and mortality, and has fiscal implications for the healthcare system [15]. It is estimated that medication harm accounts for 3.6% of all hospital admissions and occurs at an estimated rate of 10% during the inpatient stay [16]. These figures are likely to underestimate harm as there is frequent under reporting [16]. In the residential aged care setting, it is estimated that at least 14% of residents have one or more adverse drug reactions over a 12-month period [16]. Detection and classification of medication harm using causality and preventability tools have identified that up to 40% of medication harm events are preventable [17]. The World Health Organisation (WHO) has issued a global safety challenge to achieve a 50% reduction in preventable medication harm by 2022 [18].

Early identification of individuals at high risk of medication harm to whom preventive strategies are targeted can improve health outcomes and reduce healthcare costs [19]. Medication harm is especially common in older adults due to comorbidities, polypharmacy, and an age-related decline in the physiological ability to metabolise and eliminate medication [20]. If frailty is superimposed, we hypothesise that the risk of medication harm is increased, although, to the best of our knowledge, there has been no review of studies that have investigated this hypothesis. Therefore, we undertook a review of studies to determine if there is an association between frailty and medication harm.

2 Methods

This review was conducted and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) Guidelines [21]. The protocol had been registered with Open Science Framework (10.17605/OSF.IO/DMKQ4).

All articles generated from searches in the relevant databases were screened by title and abstract by two reviewers, JL and either NF or DL, to identify potentially suitable studies. Full-text review for the inclusion of the eligible studies was conducted by two reviewers (JL and NF or DL). Discrepancies were resolved through discussion and where necessary through advice from a third reviewer (MB).

Given the heterogeneous methods, results, and reporting of included studies, we chose to describe key findings narratively and categorise results in tables. The studies were grouped based on whether they reported a non-frail (also known as robust) control population, or whether they only included a frail population.

In addition to evaluating frailty and its association to medication harm, we also determined if the studies had assessed the causality, severity, and preventability using validated methods. Data extraction and reporting included the statistical analysis provided by each study such as *p* values, odds ratios, confidence intervals, risk ratios, and hazards ratios.

2.1 Inclusion Criteria

Medication harm refers to any harm or injury relating to medication use [13]. As a clear description of medication harm across some studies is lacking, we included medication harm and related synonyms such as adverse drug reactions and adverse drug events.

Studies were considered for inclusion if they stated medication harm as a primary and/or secondary outcome. Studies were also included if they appraised other secondary measures (inappropriate prescribing, medication error, and non-adherence).

Studies must have evaluated medication harm in an exclusively frail population, either as a subset of a larger population or as a cohort in which all study participants were deemed to be frail. To be included, frailty should have been clearly defined (using either tools or criteria as defined in existing literature). There were no restrictions to the study design.

2.2 Exclusion Criteria

Studies were excluded if medication harm was not reported as their primary or secondary outcome (Fig. 1), and if there was no clearly defined method for assessing frailty. Publications in languages other than English were excluded.

2.3 Information Sources and Search Strategy

A scoping literature search was undertaken in four databases from the time of database inception until 1 December 2021. The databases included PubMed, Embase, Cumulative Index to Nursing and Allied Health (CINAHL), and the Cochrane Library. Studies were identified using medical subject headings (MeSH) and keywords in the title or abstract related to medication harm and frailty. Medication harm was denoted by adverse drug event (ADE), adverse drug reaction (ADR), medication misadventure, drug-related harm, and medication-related harm. Frailty was denoted by terms within commonly used validated frailty assessment tools such as Clinical Frailty Scale (CFS)/Rockwood Frailty Score, Edmonton Frail Scale, and Fried's Frailty Index (FFI), combined with other words synonymous with frailty such as frail, frail elderly, frail syndrome using the Boolean operator 'AND.' The full search strategies for each database are included in the electronic supplementary materials (ESM; Appendix I). Google Scholar and citation searching from citations and references lists of the included studies were also undertaken to identify additional studies.

2.4 Definition of Frailty

In general, there are two broad models of frailty, which are the phenotype model [22] and the cumulative deficit model [23]. For the phenotype model [22], individuals are assessed through selected patient characteristics (e.g., unintentional weight loss, reduced muscle strength, reduced gait speed, self-reported exhaustion, and low energy expenditure); if those characteristics are present, poorer outcomes could be predicted. Individuals with three or more characteristics are considered to be frail, and others with lesser characteristics could be identified as pre-frail or robust. However, in the cumulative deficit model, individuals will accumulate deficits, including signs/symptoms/disease (e.g., loss of hearing, low mood, tremor, dementia) [6]. These deficits add to the increase in frailty index [24].

2.5 Definition of Medication Harm

Common terms used synonymously in the literature to describe medication harm include adverse drug events (ADE), adverse drug reactions (ADR), and drug-related

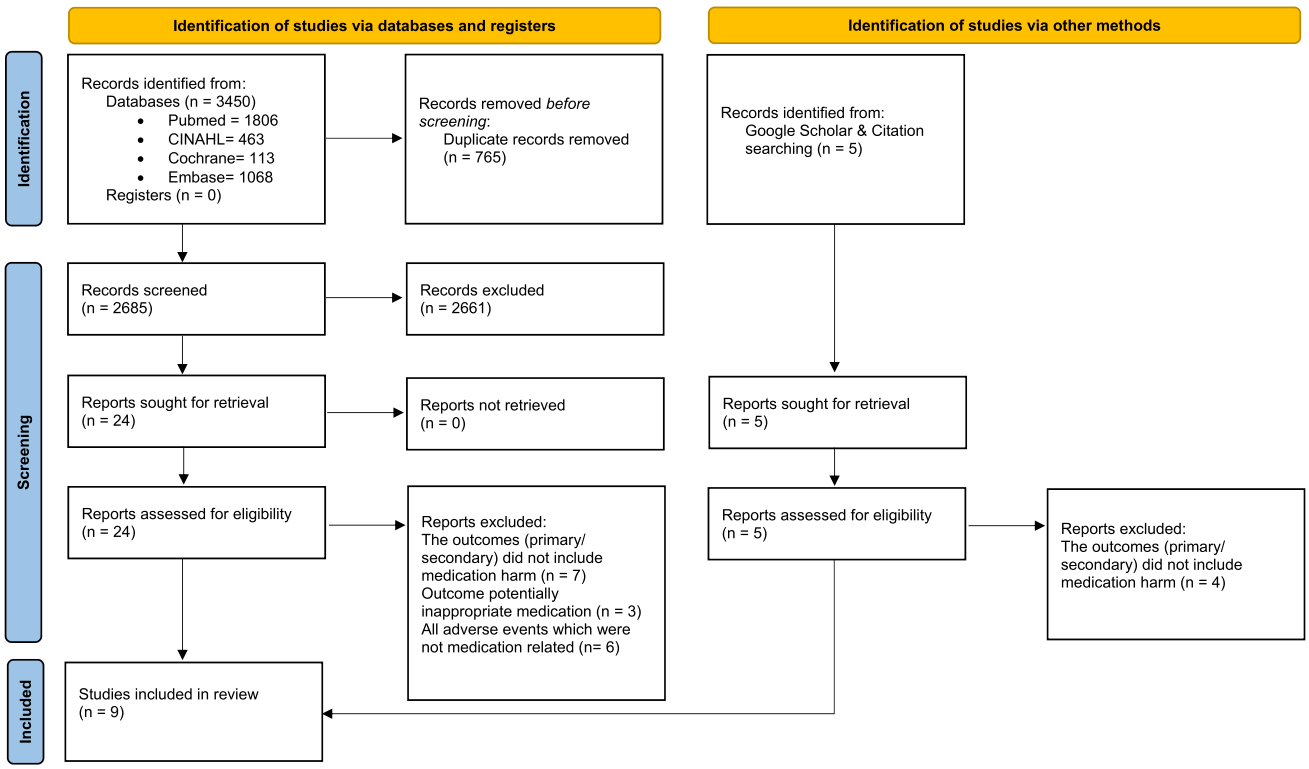

Fig. 1 PRISMA flow diagram

problems (DRPs). Terms are often used based on researcher preference and their definition can vary, in that some studies include all actual patient harm related to the use of medicine whilst others include medication errors. The different methods/definitions of each study are shown in Table 2.

ADE and ADR are commonly defined by the International Classification of Diseases (ICD-10) codes. World Health Organisation (WHO) [25] provides a clear definition of ADR as "any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function." The following definition of ADR by Edwards and Aronson [26] was adopted: "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product." Chemotherapy-related toxicity is defined using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) [27].

2.6 Assessment of Medication Harm

As medication harm is a major healthcare problem [28, 29], greater emphasis is needed to correctly identify and evaluate events. This is crucial to accurately determine harm resultant from a medication. Only then can we devise appropriate preventative strategies. There are two main methods for detection of medication harm; (1) retrospective review of medical records [30] (e.g., using coding data or a trigger tool as a starting point), or (2) prospective identification [31] (e.g., patient follow up by a trained clinician to identify medication harm close to the time it occurs). Whilst prospective methods are considered the gold standard [32] as they are likely to be more accurate, they are also more resource intensive. Retrospective detection poses a practical approach to harm detection [33]. However, all potential events should be evaluated with a comprehensive clinical record review and rated for causality (to identify a true link between the event and a medicine), severity, and preventability. Ideally, these processes should be done by trained clinicians, with multidisciplinary involvement (e.g., pharmacists, nurses, and physicians).

2.7 Assessment of Risk of Bias

The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (QATOCCS) [34] was used to critically appraise and evaluate the risk of bias for each study using the 14 key criteria. When conducting bias assessments, not all criteria were considered to be of equal importance, and a demerit point was awarded for every 'No', 'Cannot Determine' (CD), or 'Not Reported' (NR) response. For a study to receive an overall grade of 'Good' in the bias assessment, it should have two or fewer demerits; studies graded as 'Fair' had between three and six demerits; and if more than six demerits, studies were graded as 'Poor'. Criteria listed as 'Not Applicable' (NA), did not carry a demerit. This overall grading method was devised through consensus by the research team.

3 Results

3.1 Study Selection

The literature search identified 3450 studies and after removing duplicates, 2685 remained. When screening titles and abstracts, 2661 were excluded. Of the 24 studies that remained, full-text articles were assessed for eligibility, and 15 were excluded. The remaining nine articles investigated medication harm in frail patient cohorts (using clearly defined criteria or validated measurements of frailty) and were included in the final review (Fig. 1)

An updated literature search (1 December 2021) undertaken has identified 206 (PubMed), 63 (CINAHL), 55 (Cochrane), and 235 (Embase) additional results. Of the identified 559 studies, duplicates were removed, and 408 remained. Four studies went through a further full-text review for eligibility, and none were included. The main reason for exclusion was that medication harm was not the primary/secondary outcome.

3.1.1 Study Design

The characteristics of the nine studies are shown in Table 1. Three studies used a retrospective cohort design (Cheong et al. [35], Cullinan et al. [36], Guo et al. [37]), and the remaining six studies (Athuraliya et al. [38], Stevenson et al. [39], Ruiz et al. [40], Schmader et al. [41] Hanlon et al. [42], Ekerstad et al. [43]) used a prospective design.

3.1.2 Study Characteristics

Four studies were conducted in the United States [37, 40–42], one in Singapore [35], one in Ireland [36], one in Australia [38], one in the United Kingdom (UK) [39], and one in Sweden [43]. Studies were conducted across different healthcare settings. Two studies included both inpatient and outpatient cohorts [37, 41], one study comprised only men in the community setting [38], three studies comprised only outpatient clinic attendees [35, 40, 42], and three only inpatients [36, 39, 43]. The mean age of study participants ranged from 65.5 to 89.7 years.

3.1.3 Study Gender

Three studies [35, 37, 43] reported having a greater proportion of female participants whilst four studies [39–42] reported more males in their study cohort. The study by Athuraliya et al. [38] aimed to examine the association of frailty with medication-related hospitalisation in community-dwelling older men, and therefore 100% of enrolled participants identified as males. One study [36] did not report any gender data.

Two studies [41, 42] used the same population with Schmader et al. [41] reporting no significant difference between genders ($p = 0.78$). The study by Ruiz et al. [40] specifically recruited individuals receiving palliative therapy for non–small-cell lung cancer (NSCLC). This may explain why they recruited more males, with men having a higher rate of tobacco smoking, a key risk factor for NSCLC [40].

3.1.4 Study Sample Size

All included studies reported sample sizes, which ranged from 50 to 37,799 participants. As six studies [35–40] comprised both frail and non-frail populations, sample size calculations would have been desirable in determining if the study had the required power to identify the pre-specified differences between the groups if they existed. However, only one study [35] reported a sample size calculation. Four studies [35, 36, 40, 43] indicated that the results of their findings may have been negatively impacted due to the small sample size and underpowered studies.

3.1.5 Study Setting

Four studies [35, 36, 39, 43] were conducted in the hospital inpatient setting, and two [40, 42] in hospital outpatient settings. The study by Ruiz et al. [40] and Hanlon et al. [42] were conducted in oncology outpatient clinics and veteran affairs medical centres, respectively. Two studies [37, 41] were conducted in both hospital inpatient and outpatient settings. Only one study [38] was conducted in a community setting where participants were from a population-based longitudinal study (Health In Men Study) identified from an electronic copy of the electoral roll [44].

3.1.6 Definition and Measurement of Frailty

The Clinical Frailty score developed by Rockwood et al. [23] presents the degree of frailty on a scale ranging from 1 to 9 (very fit to terminally ill). The FRAIL scale [45] consists of five domains: fatigue, resistance, ambulation, illness, and loss of weight. Each domain is given a score of 1 if it is present and individuals scoring ≥ 3 points are considered to be frail. The Frail Elderly Support Research (FRESH) group screening instrument [46] is an example that was developed based on the Fried phenotype model [22] with the addition of visual and cognitive impairment in the assessment. Individuals are determined to be frail if they meet ≥ 3 of the frailty indicators.

An example of the cumulative deficit model is the Fried frailty phenotype which considers the use of 21 variables to calculate predicted frailty probability with a cut-off score [47] and this score can be further specified to classify individuals with ≥ 0.20 as frail. Frailty measures could also be self-defined and not with modification or guidance of existing frailty tools. Some are assessed based on dependence in at least one activity of daily living [ADL], stroke within 3 months, previous falls, difficulty ambulating, malnutrition, dementia, depression, unplanned admission in the last 3 months, prolonged bed rest, or incontinence [41, 42]. Frailty is determined by meeting two out of the ten criteria.

The nine included studies utilised different methods, tools, and definitions in assessing frailty in the population. Six studies [35, 37–40, 43] reported using a validated frailty assessment to identify frailty. Cheong et al. [35] used the CFS, which is a validated measure by Rockwood et al. [23], which was able to predict the length of hospitalisation, functional decline, and 30-day outcome (readmission and mortality) after discharge with good reliability [48, 49]. Cullinan et al. [36] constructed a frailty index based on the Rockwood frailty index. However this was not validated [50]. Guo et al. [37] have used a validated algorithm that was developed based on the Fried frailty phenotype. The phenotype uses latent class analysis to internally validate theoretical construct, demonstrating high internal construct validity [51], and predictive validity was assessed [47]. Athuraliya et al. [38] used the FRAIL scale and this was internally validated in the same cohort of the Health In Men Study (HIMS) based on its predictive validity instead of construct validity [52].

Stevenson et al. [39] used a frailty index, which was internally validated using Kaplan–Meier analysis to evaluate the relationship between frailty and mortality [50]. Ruiz et al. [40] measured frailty phenotype using the Fried frailty index, which was validated and supported by other studies [22, 51, 53] on its concurrent and predictive validity. Two studies [41, 42] used non-validated self-defined criteria where they classified individuals as frail if they met two or more of the following ten criteria: dependence of at least one activity of daily living, stroke within 3 months prior to hospitalisation, previous falls, difficulty ambulating, malnutrition, dementia, depression, unplanned admission in the last 3 months, prolonged bed rest, or incontinence. Ekerstad et al. [43] used the Frail Elderly Support Research group screening instrument in evaluating frailty, supported by a study on its construct validity [46].

Table 1 Study characteristics

Study	Title	Country	Setting	Population				Sample size	Study cohort	
				Frail	Non frail	Age (years)	Gender		Design	Dates
Cheong et al. [35]	The prevalence of frailty and its association with adverse drug reactions in hospitalized older adults	Singapore	Geriatric outpatient/emergency department	83.3%	16.7%	Mean 89.7 ± 4.0	M: 35% F: 65%	150	RC	From Sep 2016
Cullinan et al. [36]	Use of a frailty index to identify potentially inappropriate prescribing and adverse drug reaction risks in older patients	Ireland	Hospital inpatient	51.2%	48.8%	Median 77 IQR 71–83	NR	711	RC	Jun 2012 to Jun 2013
Guo et al. [37]	Safety and effectiveness of apixaban compared with warfarin among clinically relevant subgroups of venous thromboembolism patients in the United States Medicare population	USA	Hospital inpatient/outpatient	45.1%	54.9%	Mean 78	M: 37% F: 63%	37,799	RC	1 Mar 2014 to 31 Dec 2016
Athuraliya and Etherton-Beer [38]	Health in Men Study: is frailty a predictor of medication related hospitalization?	Australia	Community dwelling	13.2%	86.8%	Mean 75.6 ± 5.9	M: 100%	4324	PC	2001 to 2004
Stevenson et al. [39]	Frailty is a predictor of medication-related harm requiring healthcare utilisation: a multicentre prospective cohort study	UK	Hospital inpatient	40%	60%	Median 81.9 IQR 75.5–86.9	M: 58.4% F: 41.6%	1112	PC	Sep 2013 to Nov 2015
Ruiz et al. [40]	Frailty assessment predicts toxicity during first cycle chemotherapy for advanced lung cancer regardless of chronologic age	USA	Oncology outpatient	27.1%	72.9%	Mean 68.5 ± 9.5 IQR 75.5–86.9	M: 79.2% F: 20.8%	50	PC	Oct 2010 to Apr 2014
Schmader et al. [41]	Effects of geriatric evaluation and management on adverse drug reactions and suboptimal prescribing in the frail elderly	USA	Geriatric inpatient/outpatient	100%	×	46% population aged 65–73 54% ≥74	M: 98% F: 2%	864	PC	31 Aug 1995 to 31 Jan 1999

Table 1 (continued)

Study	Title	Country	Setting	Population		Age (years)	Gender	Sample size	Study cohort	
				Frail	Non frail				Design	Dates
Hanlon et al. [42]	Incidence and predictors of all and preventable adverse drug reactions in frail elderly persons after hospital stay	USA	Hospital outpatient	100%	×	46.4% >75	M: 98% F: 2%	808	PC	31 Aug 1995 to 31 Jan 1999
Ekerstad et al. [43]	Early rehospitalizations of frail elderly patients – the role of medications: a clinical, prospective, observational trial	Sweden	Hospital inpatient	100%	×	Mean 85.7	M: 43% F: 57%	390	PC	Mar 2013 to Jul 2015

F Female, *IQR* interquartile range, *M* male, *NR* not reported, *PC* prospective cohort, *RC* retrospective cohort, *USA* United States of America, *UK* United Kingdom, × none, ± tolerance range

3.1.7 Definition and Measurement of Medication Harm Events

In this review, six studies (Guo et al. [37], Stevenson et al. [39], Ruiz et al. [40], Schmader et al. [41], Hanlon et al. [42], and Ekerstad et al. [43]) provided a clear definition of what constituted medication harm. Table 2 describes the key term used by each study for their measure of medication harm, as well as how harm was defined and measured. Nine studies [35–43] included ADRs as part of their outcome definition, two of which included harm from non-adherence to medications [39, 43]. Additionally, Stevenson et al. [39] included medication errors that resulted in actual medication harm.

Of the remaining four studies, three [35, 36, 42] did not provide any definition for the outcome of medication harm/ADR. Cheong et al. [35] provided no definition for ADRs or indeed how these ADRs were detected but did describe conducting a causality analysis using the Naranjo algorithm, and severity using the Hartwig criteria. Cullinan et al. [36] clearly detailed the identification of potentially inappropriate prescribing using the STOPP/START criteria (Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert to Right Treatment) but failed to describe how ADRs were identified.

Two studies [41, 42] were based on the same study population. Schmader et al. [41] focused on the impacts of ADR by comparing events in groups of patients receiving geriatric care and usual inpatient care. Hanlon et al. [42] assessed the causality and preventability of ADR in the study population after a hospital stay. Hanlon et al. [42] did not report a definition of what constituted an ADR but did describe causality analysis based on assessments by blinded pairs of geriatrician and geriatric pharmacist.

The study by Athuraliya et al. [38] did not provide a clear definition of the primary outcome of ADEs but reported a wide range of International Classification of Disease version-10 (ICD-10) coded adverse events (both medication related and potentially medication related, e.g., renal failure). ICD-10 Y codes are synonymous with harm as a result of medication use and are identified and assigned to hospitalisations by clinical coding teams, generally for hospital financial reimbursement. Whilst a good crude measure of medication harm, the reliability of coding can be variable, for example depending on the expertise of the clinical coders and the accuracy of documentation in patient notes. A limitation of this study was the lack of clinical verification (i.e., review of patient records retrospectively) of the ICD-10 codes to confirm an actual medication harm event had taken place. Therefore, Athuraliya et al. [38] used the term 'potential' medication harm as they did not perform a subsequent causality analysis to confirm the coding data. A retrospective review of clinical coding data is a pragmatic method

for detecting medication harm in large data sets but must be coupled with a robust clinical record review to confirm causality [54].

Guo et al. [37] defined medication harm to be bleeding and recurrent venous thromboembolism (VTE), also using a standard list of ICD codes to identify major bleeding (ICD-9) and recurrent VTE (ICD-10). They reported similar limitations, including that identification of medication harm using ICD codes may differ from the clinical diagnostic tools used in clinical trials. The study by Ruiz et al. [40] used toxicity as the measure of medication harm and applied a modified geriatric assessment risk score using cut offs for variables such as age (≥ 72 years), haemoglobin (b11 g/dL for men, b10 g/dL for women), creatinine clearance (< 34 mL/min per Jeliffe calculation), hearing impairment (fair or worse), number of falls in last 6 months (≥ 1), assistance with medications, limitation in walking one block, and decreased social activity because of physical/emotional health to determine the grade of toxicity from chemotherapy.

3.2 Causality Analysis

Five studies [35, 39, 41–43] rated causality between medication use and harm using tools comprising the Naranjo algorithm [55], Hallas criteria [56], and physician–pharmacist pairs using clinical judgement [57]. In the only study that used more than one tool concurrently, Ekerstad et al. [43] found rates of causality for the Naranjo scale [55], clinical judgement, and Hallas criteria [56] differed significantly: 9.4%, 13.5%, and 2.1%, respectively.

3.2.1 Severity

Only three studies [35, 39, 41] assessed the severity of ADRs, with Cheong et al. [35] employing the Hartwig and Siegel criteria [58] according to the clinical outcomes. Stevenson et al. [39] graded the severity of medication harm using the approach of Morimoto et al. [59]. Lastly, Schmader et al. [41] used the clinical judgement of a trained clinical pharmacist based on chart review or patient interview. The severity assessment is important to guide clinicians to carry out interventions based on the level of severity (e.g., minor, moderate, severe) [60].

3.2.2 Preventability

Three studies [39, 42, 43] reported preventability of medication harm, one based on consensus clinical judgement of an expert panel of physicians and pharmacists [42], and the others using the Hallas criteria with research pharmacists for cross-site case discussions [39] or with two independent clinicians to determine the preventability of hospital admissions [43].

3.2.3 Study Outcomes

Study outcomes relating to medication harm included medication-related hospitalisation, appropriateness of medications, chemotherapy-related toxicity, the incidence of major bleeding, clinically relevant non-major bleeding (CRNM), recurrent venous thromboembolism, and mortality (Table 3). Medication harm (e.g., ADE, ADR, other synonymous terms) was the primary outcome in eight studies [35, 37–43] and the secondary outcome in two studies [36, 37].

3.2.4 Frail and Non-Frail Populations

Six studies [35–40] included two groups of participants, one with frail and one without frail participants (or a so-called robust group). Cheong et al. [35] reported the prevalence of frailty as 83.3%, of whom 70% experienced more than one ADR, with more than 40% of the ADRs being mild to moderate in severity. The outcome of ADR experienced in each body system, namely cardiovascular, central nervous, endocrine, gastrointestinal, haematology, and renal was compared between the frail and robust group. Cheong et al. [35] found a higher incidence of medication harm related to cardiovascular medications in robust individuals compared to frail individuals (48% vs 24%, $p = 0.03$). However, the reverse was true for central nervous system medications where adverse events were more common in the frail (18.4%) than in robust individuals (18.4% vs 0%, $p = 0.02$).

Cullinan et al. [36] reported that patients who were deemed frail were twice as likely to develop ADRs (OR 2.6, CI 1.474–3.044, $p < 0.0001$) although the type of ADR was not explored. Even though the effect of experiencing ADRs was significant, the study failed to adjust for confounders such as polypharmacy. For a secondary outcome, Cullinan et al. [36] reported a significant correlation between FI score and potentially inappropriate prescribing (PIP), with frail individuals twice as likely to receive PIP (OR 2.1, CI 2.0–3.6, $p < 0.0001$).

Guo et al. [37] reported a large cohort size ($N = 37799$), comparing patients receiving apixaban vs warfarin. Among patients taking apixaban, frailty was associated with a 15% (HR 0.85, 95% CI 0.75–0.97) lower risk of CRNM bleeding, while non-frailty was associated with 32% lower risk (HR 0.68, 95% CI 0.59–0.78), as compared with patients taking warfarin. Apixaban was also associated with a lower risk of major bleeding and clinically CRNM, and a similar risk of recurrent venous thromboembolism as compared with warfarin (p values not reported), although there were no distinct comparisons between the frail and robust groups. Guo et al. [37] conducted 1:1 propensity score matching without

Table 2 Medication harm definitions and causality analysis methods

Study	Frailty screening assessments	Medication harm terminology	Medication harm definition	Method of detection and review	Causality analysis tool
Cheong et al. [35]	Clinical Frailty Scale	ADRs	No definition, but 'side effects' of medication included and causality appraised using Naranjo	NR Did report causality and severity analysis using validated tools	Naranjo ADR Probability Scale
Cullinan et al. [36]	Frailty index	ADRs	NR	NR	NR
Guo et al. [37]	An algorithm based on Fried frailty phenotype	Bleeding and recurrent VTE with warfarin and apixaban	Defined according to validated set of ICD-9/10 codes. Clear definition of included conditions provided	ICD-9/10 codes in retrospective dataset	NR
Athuraliya and Etherton-Beer [38]	FRAIL scale	ADEs	Defined according to ICD-10 codes	Retrospectively identified using a range of ICD-10 codes but not verified through chart review to confirm that the coding was appropriate	NR
Stevenson et al. [39]	Frailty index	Medication related harm (MRH)	"Adverse drug reactions and a failure to receive medication, either following non-adherence or a failure in the supply chain" based on 1990 definition of DRPs by Strand et al. [82]	Patients followed post-hospital discharge for 8 weeks: MRH identified through patient interviews and GP records Independent panel with geriatrician and professor of clinical pharmacy	Naranjo ADR Probability Scale (Consultant geriatrician & professor of clinical pharmacy)
Ruiz et al. [40]	Fried Frailty Index	Toxicity	Defined using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) [27]	Confirmed by two clinicians' clinical judgement using CTCAE	NR
Schmader et al. [41]	Specific frailty criteria (2 out of 10 stated criteria)	ADRs	WHO [25]	Blinded reviewers from group allocation (Geriatric vs usual care)	Naranjo's algorithm & blinded physician–pharmacist pairs
Hanlon et al. [42]	Specific frailty criteria (2 out of 10 stated criteria)	ADRs	NR	Measured by pharmacists, case summarised and presented to a panel of blinded clinicians for causality assessment	Naranjo's algorithm & blinded geriatrician and geriatric pharmacist pairs
Ekerstad et al. [43]	Frail Elderly Support Research (FRESH) group screening instrument	ADRs and absence of evidence-based treatment constituting to rehospitalisation	Edwards and Aronson [26]	Early rehospitalisation within 30 days was rated by 2 senior clinicians to determine medication related, non-medication related or underuse of medication	Naranjo scoring & Hallas criteria & clinical judgment (two independent clinicians & third independent clinician to resolve discordance

ADE Adverse drug events, *ADR* adverse drug reactions, *CTCAE* Common Terminology Criteria for Adverse Events, *ICD* International Classification of Disease, *MRH* medication-related harm, *NR* not recorded, *VTE* venous thromboembolism, *WHO* World Health Organisation

replacement to balance baseline demographic and clinical characteristics between patients who were on apixaban as compared to warfarin.

Athuraliya et al. [38], found that frail men were at a higher risk of experiencing an ADR (OR 3.15, 95% CI 2.49–3.97, $p < 0.001$), ADE related hospitalisation (OR 6.83, CI 4.91–9.51) and mortality at 24 months (OR 3.14, 95% CI 2.28–4.33) compared to non-frail individuals. They [38] reported a significant association between frailty and medication harm-related outcomes and results were adjusted for several confounders including age, smoking status, and comorbidity, but not for polypharmacy.

Stevenson et al. [39] reported a significant relationship between medication-related harm and frailty (OR 10.06, 95% CI 2.06–49.26, $p = 0.004$), after adjusting for age, gender and polypharmacy. They also reported that with increasing polypharmacy, healthcare utilisation rates due to medication harm increased from 20 to 40%.

Ruiz et al. [40], reported that 27% of their oncology cohort were frail (FFI criteria ≥ 3). Of the frail population, 77% experienced grade 3–5 toxicity, and 23% experienced a grade 0–2 toxicity during the first cycle of chemotherapy (OR 7.03, 95% CI 1.11–44.5). They also demonstrated that FFI is a significant predictor of grade 3 or higher toxicities in the model which was adjusted for gender and current smoking at baseline (OR 10.22, 95% CI 1.24–84.27) in all patients who completed the second cycle of chemotherapy.

3.2.5 Frail Only Population

Three studies [41–43] only recruited frail patients, precluding any direct comparison in outcomes according to frailty. Schmader et al. [41] reported that outpatient geriatric management reduced serious ADR as compared with usual care, and geriatric management in both inpatient and outpatient settings reduced suboptimal prescribing. They also reported specialised geriatric outpatient clinics reduced the incidence of serious ADRs by 35% compared to usual outpatient care ($p < 0.05$).

The prospective study by Hanlon et al. [42] reported that 33% of participants experienced at least 1 ADR and 16% of the participants experienced at least 1 preventable ADR. ADRs are more common in frail elderly especially after hospitalisation, and in those with polypharmacy and receiving warfarin. Frail participants taking warfarin were at a 50% increased risk of ADR compared to participants not on warfarin (adjusted HR 1.51, 95% CI 1.22–1.87, $p < 0.001$).

Ekerstad et al. [43] reported that independent risk predictors for early rehospitalisation in their cohort were heart failure (OR 1.8, 95% CI 1.1–3.1) and anaemia (OR 2.3, 95% CI 1.3–4.0).

3.3 Risk of Bias

Using the QATOCCS [34] to categorise studies as "good (0-2 demerits), fair (3-5 demerits), or poor (≥ 6 demerits)", the average number of demerits across studies was 4 points, indicating fair quality (Table 4), with demerits relating to lack of reporting of methods or results.

Only two of the nine studies [41, 43] met the criteria for "good" suggesting a low risk of bias, with limitations from failure to: examine the effects in different levels of medication exposure (i.e., drug dosage: low/medium/high dose) [41, 43]; to assessing medication harm more than once during the course of the study period [41, 43]; and not reporting if assessors were blinded from ADR assessment, and non-adherence contributing to rehospitalisation, when applying assessment tools [43]. However, examining medication effects from different levels of medication exposure is often not feasible in medication harm studies. The major strengths of these two studies [41, 43] were clear research aims; adjustment for confounders in predicting ADR and early rehospitalisation risk respectively; and sufficient timeframe to determine the association between the exposure and outcome. Schmader et al. [41] measured hospitalisation as the study outcome and allocated 12 months follow up after randomisation to ensure the association between the different types of care (geriatric/usual) and hospitalisation were appropriately examined. As early rehospitalisation was the study outcome, the authors [43] defined medication-related rehospitalisation within 30 days of discharge, which allowed a sufficient timeframe to assess the association between frailty and early rehospitalisation.

Six studies [35, 37–40, 42] were rated as "fair". Among the studies that were rated "fair", had similar limitations as those rated as "good". Additionally, other common limitations include the lack of sample size justification and consideration of timeframe to reasonably identify medication harm from medication exposure. One study [36] was rated as "poor" due to unclear specification of the study population according to explicit selection criteria, lack of documentation on what adverse outcomes the study team considered to be ADR, and failure to adjust for potential confounders (polypharmacy).

3.4 Medications and Associated Harm Events

The types of harm and classes of medicines involved are listed in Table 5. Five studies [35, 38, 41–43] reported CVS medications which included classes such as angiotensin-converting-enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), beta-blockers, calcium channel blockers, and digoxin. Two studies involved specific medication classes: Guo et al. [37] studied anticoagulants (apixaban and warfarin) and Ruiz et al. [40] studied the

Table 3 Study outcomes

Study	Outcome measurements		Groups		Study outcomes		
	Primary	Secondary	Intervention	Control	Frail	Robust	Statistical significance
Frail and non-frail (robust) population							
Cheong et al. [35]	ADRs	Severity of ADR	Frail	Non-frail	Cardiovascular 24%	Cardiovascular 48%	$p = 0.03$
					CNS 18.4%	CNS 0%	$p = 0.02$
					Endocrine 7.2%	Endocrine 4%	$p = 0.70$
					Gastrointestinal 41.6%	Gastrointestinal 40%	$p = 1.00$
					Haematology 12.8%	Haematology 16%	$p = 0.72$
					Renal 28.8%	Renal 40%	$p = 0.34$
Cullinan et al. [36]	Appropriateness of medications: PIP	ADR occurrence	Frail	Non-frail	Experiencing at least 1 ADR 29.4%	Experiencing at least 1 ADR 16.7%	OR 2.1, 95% CI 1.474–3.044; $p < 0.0001$
Guo et al. [37]	Major bleed and recurrent VTE	CRNM bleeding	Frail	Non-frail	Major bleeding HR 0.80	Major bleeding HR 0.69	$p = 0.440$
					CRNM bleeding HR 0.85	CRNM bleeding HR 0.68	$p = 0.015$
					Recurrent VTE HR 0.99	Recurrent VTE HR 1.09	$p = 0.752$
Athuraliya and Etherton-Beer [38]	ADR-related hospitalisation	All cause of hospitalisation and mortality	Frail	Non-frail	ADE 18.71%	ADE 6.82%	OR 3.15, 95% CI 2.49–3.97; $p < 0.001$
					ADE-related hospitalisation 18.7%	ADE-related hospitalisation 6.8%	OR 6.83, 95% CI 4.91–9.51 *p* values not reported
					Non-ADE-related hospitalisation 71.9%	Non-ADE-related hospitalisation 69.4%	OR 2.63, 95% CI 2.01–3.45 *p* values not reported
					Mortality (12 mo) 3.5%	Mortality (12 mo) 1.2%	OR 2.97, 95% CI 1.79–4.92 *p* values not reported
					Mortality (24 mo) 9.2%	Mortality (24 mo) 3.1%	OR 3.14, 95% CI 2.28–4.33 *p* values not reported
Stevenson et al. [39]	Medication-related harm (MRH) relating to ADR, non-adherence, and medication error	NR	Frail	Non-frail	MRH 10 times more likely in frail than robust population		OR 10.06, 95% CI 2.06–49.26; $p = 0.004$
Ruiz et al. [40]	Treatment toxicity for chemotherapy	Dose delay/reduction attributed by toxicity and unplanned hospitalisation	Frail	Non-frail + pre-frail	Grade 3–5 toxicity (1st cycle of chemotherapy) 77%	Grade 3–5 toxicity (1st cycle of chemotherapy) 23%	OR 7.03, CI 1.11–44.5 *p* values not reported
					Grade 0–2 toxicity (1st cycle of chemotherapy) 43%	Grade 0–2 toxicity (1st cycle of chemotherapy) 57%	NR

Table 3 (continued)

Study	Outcome measurements		Groups		Study outcomes		
	Primary	Secondary	Intervention	Control	Frail	Robust	Statistical significance
Frail-only population							
Schmader et al. [41]	ADRs and serious ADRs	PP, inappropriate prescribing, and underuse	Frail	No control	All ADR 64–206 number of events per 1000 days	NA	RR 1.85, 95% CI 1.40–2.45 $p = 0.0001$
					Serious ADR 15–27 number of events per 1000 days	NA	RR 1.03, 95% CI 0.55–1.95 $p = 0.93$
Hanlon et al. [42]	ADRs	NR	Frail	No control	≥ 1 ADR 33% ≥ 1 Preventable ADR 16%	NA	Independent risk factors for ADRs Number of medications HR 1.07, 95% CI 1.05–1.10 per medication Use of warfarin HR 1.51, 95% CI 1.22–1.87 Use of benzodiazepines HR 1.23, 95% CI 0.95–1.58 Use of sedatives and/or hypnotics was inversely related to ADR risk HR 0.14, 95% CI 0.04–0.57
Ekerstad et al. [43]	Early rehospitalisation due to ADR	Early rehospitalisation due to underuse	Frail	No control	*ADR cause of rehospitalisation* Naranjo scale 9.4% Clinical judgement 13.5% Hallas criteria 2.1%	NA	NA

ADL Activities of Daily Living, *ADR* adverse drug reaction, *AKI* acute kidney injury, *CFS* Clinical Frailty Scale, *CNS* central nervous system, *CRNM* clinically relevant non-major, *CTCAE* Common Terminology Criteria for Adverse Events version 4.0, *HR* hazards ratio, *MB* major bleeding, *MRH* medication-related harm, *NA* not applicable, *NCI* National Cancer Institute, *NR* not reported, *OR* odds ratio, *PP* polypharmacy, *p p* value, *PIP* potentially inappropriate prescribing, *RR* risk ratio, *VTE* venous thromboembolism, *WADLS* Western Australia Data Linkage System, *95% CI* 95% confidence interval

adverse effects of chemotherapy. Cullinan et al. [36] and Stevenson et al. [39] did not report the type or incidence of medication harm.

Among the nine studies, five studies [35, 37, 38, 40, 41] quantified the medication harm by listing the drug and/or the drug class that contributed to the medication harm (e.g., non-steroidal anti-inflammatory drugs & ACEI causing acute kidney injury). However, only Cheong et al. [35] reported the specific rates of medication harm to individual organ systems (cardiovascular, central nervous system, endocrine, gastrointestinal, haematology, renal) between the individual frail and non-frail populations. The study by Athuraliya et al. [38] observed that benzodiazepines and antihistamines were more commonly used among frail men. The other three studies [37, 40, 41] did not report the specific medication/medication class associated with each medication harm that was listed. The remaining four studies [36, 39, 42, 43] did not quantify medication harm by listing medications that contribute to an ADR.

Cheong et al. [35], Guo et al. [37], and Ekerstad et al. [43] reported the correlation between harm and the suspected medication. Three studies [38, 41, 42] listed the medications and medication harms, but without reporting a statistical association. Ekerstad et al. [43] also reported that underuse of evidence-based drug treatment could have a similar impact to ADR in leading to patient rehospitalisation, which affected 19.8% of patients.

The most common type of medication harm was cardiovascular ADRs, reported in six studies [35, 37, 40–43], with the second most common event being bleeding, reported in four studies [35, 37, 41, 43], and kidney injury, reported in four studies [35, 38, 41, 42]. Guo et al. [37] and Ruiz et al. [40] investigated anticoagulant and chemotherapy treatment, respectively. Therefore, the medication involved in both studies may not be indicative of the medications that are generally used in the geriatric population.

4 Discussion

This scoping review identified nine studies evaluating medication harm in frail patients, of which five [35–39] showed frailty has a statistically significant association with medication harm. Six studies [35–40] included both frail and non-frail cohorts, and three studies were conducted in a frail-only population. Only six studies [37–41, 43] performed statistical adjustments for baseline characteristics (i.e., age, gender, smoking status, comorbidity) and were independently correlated with medication harm. As polypharmacy is more prevalent in frail individuals compared with non-frail individuals [61], not statistically adjusting for polypharmacy may lower the internal validity of the studies, which reduces the generalisability of findings. Without adjusting for confounders, studies could only provide a crude association of frailty with medication harm. However, of the nine studies, only one [39] incorporated polypharmacy in their logistic regression model and was able to report the significant association of frailty with medication harm independent of the number of medications. Polypharmacy is a known variable that could potentially cause medication harm, making it inconclusive to determine if the association between medication harm and frailty was due to the presence of polypharmacy. We stress the need to use a multivariate analysis to determine the relationship between each variable's contribution to frailty/medication harm.

4.1 Study Design and Characteristics

All nine studies used an observational study design. To best evaluate frailty as an independent risk factor for medication harm, a prospective cohort study recruiting both frail and robust patients with a justified sample size would be optimal. It should use sound methods for the detection of medication harm, incorporate other influential variables (e.g., polypharmacy) and adjust for key confounders to determine if frailty is independently associated with medication harm.

In our review, the mean patient age ranged from 65.5 to 89.7 years old. To date, studies of frailty are predominantly in older cohorts, and older age has been associated with both increased frailty and medication harm [12, 20]. However, younger adults are also at risk of both frailty and medication harm [62], and hence excluding younger individuals may not accurately portray the association of frailty with medication harm [63]. In a review, Spiers et al. [64] found no frailty measures that were designed and validated to identify frailty exclusively in young individuals (18–59 years old). Most existing literature evaluating frailty includes older participants [65, 66], and little is known about the prevalence of frailty and adverse outcomes in younger populations.

4.2 Definitions of Frailty

A gold standard method for frailty measurement has not been determined [67]. In our review, seven different assessment methods/tools were used to measure frailty. These methods included the phenotypic models [37] frailty index (accumulation of health deficits) [36, 39, 40], CFS [35], FRAIL scale [38], Frail Elderly Support Research (FRESH) group screening instrument [43], and self-defined assessment [41, 42]. This makes the comparison of frailty challenging, in particular where self-defined tools were used [41, 42]. A recent review evaluating 35 frailty scores found that agreement between frailty measures varies widely (measured using Cohen's Kappa), and that agreement was highest with an accumulation of deficit-type scores [68]. This heterogeneity makes comparing research across studies of

Table 4 Risk of bias assessment using Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (QATOCCS)

Criteria	Study								
	Cheong et al. [35]	Cullinan et al. [36]	Guo et al. [37]	Athuraliya and Etherton-Beer [38]	Stevenson et al. [39]	Ruiz et al. [40]	Schmader et al. [41]	Hanlon et al. [42]	Ekerstad et al. [43]
Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the study population clearly specified and defined?	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the participation rate of eligible persons at least 50%?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were all the subjects selected from the same or similar populations. Were inclusion and exclusion criteria for being in the study prespecified and uniform across participants?	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes
Was a sample size justification, power description, or variance and effect estimates provided?	Yes	No	No	No	Yes	Yes	Yes	No	Yes
For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	CD	CD	Yes	Yes	CD	CD	Yes	CD	Yes
For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome?	No	No	No	No	No	No	No	No	No
Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the exposure(s) assessed more than once over time?	NA	NA	NA	NA	NA	Yes	NA	NA	NA

Table 4 (continued)

Criteria	Study								
	Cheong et al. [35]	Cullinan et al. [36]	Guo et al. [37]	Athuraliya and Etherton-Beer [38]	Stevenson et al. [39]	Ruiz et al. [40]	Schmader et al. [41]	Hanlon et al. [42]	Ekerstad et al. [43]
Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Were the outcome assessors blinded to the exposure status of participants?	NR	NR	NR	NR	NR	NR	Yes	Yes	CD
Was loss to follow-up after baseline 20% or less?	Yes	Yes	Yes	Yes	Yes	Yes	CD	Yes	Yes
Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	No	No	Yes	Yes	Yes	Yes	Yes	CD	Yes
QATOCCS quality rating	Fair	Poor	Fair	Fair	Fair	Fair	Good	Fair	Good

CD Cannot determine, *NA* not applicable, *NR* not reported

frail populations difficult. Even though there is no standardised method for selecting a frailty tool [50], researchers should utilise a validated measure to ensure reliability and enhance the generalisability of their findings. Future work should seek to endorse an established, validated tool to measure and report frailty in clinical research that can be easily applied across care settings. This will also assist with quantifying frailty as part of routine clinical care (e.g., in hospitals), where it may be incorporated within a risk prediction model to prioritise high-risk patients for timely and targeted interventions by the multidisciplinary team [69]. With the increasing availability of real-time electronic patient data, risk prediction models are an emerging area of research that present a potential intervention to improving patient safety [70].

4.3 Evaluating Medication Harm

Studies in our scoping review show that frailty has a significant association with poor medication outcomes (i.e., hospitalisation, toxicity, bleeding), and an increased risk of medication harm in frail versus non-frail cohorts. However, in studies that enrolled only frail populations, a comparison cannot be made with non-frail individuals, and these studies are only suitable as a broad guide for the incidence of medication harm in frail individuals. A study [71] investigating the association between frailty measures in predicting mortality, nursing home transfer, and hospitalisation has reported similar limitations in study design, with a lack of non-frail participants limiting the generalisability of their findings.

Overall, studies reported a wide range of medication harm event rates, likely due to differences in methods of measurement, a lack of consensus in definitions for harm, and limited guidelines for data collection in this field. Similar disparities in event rates have been reported by other studies related to medication harm [14, 72]. We urge key safety bodies to lobby for the harmonisation of metrics in this area to facilitate robust research.

4.4 Medications and Associated Harm

To obtain a true sense of the incidence of medication harm, it is important to capture information on the frequency and types of medicines that were prescribed for the cohort. Whilst most studies [35, 37, 38, 40, 41] included information on types of medications that resulted in harm, there was no information on the frequency of prescribing. This limitation should be addressed in future research in this area.

Table 5 Medications and associated harm

Study	Medication harm	Frequency of medication harm (%)	Medications/classes of medications involved	Frequency of medications/classes involved (%)
Cheong et al. [35]	Constipation	41.3	Calcium	12.8
	Acute kidney injury	31	ACEI/ARB	11.2
	Delirium	21	Diuretics	8.2
	Bradycardia	21	Antiplatelets	6.9
	Postural hypotension	17	Opioids	6.9
	Hypokalaemia	16	Beta blocker	6.6
	Thrombocytopenia	15	Iron	6.6
	Hyponatraemia	13	Calcium channel blockers	4.9
	Bleeding	11	Steroids	3.3
	Hypotension	11	Antihistamines	2.3
	Hyperglycaemia	6	Others (NR)	30.3
	Deranged liver function	5		
	Hypoglycaemia	4		
	Diarrhoea	3		
Cullinan et al. [36]	NR	NR	NR	NR
Guo et al. [37]	Clinically relevant non-major bleeding Major bleeding Recurrent VTE	NR	Apixaban Warfarin	NR
Athuraliya and Etherton-Beer [38]	Acute kidney injury Delirium Mortality Non-accidental falls	NR	ACEI, ARB Beta blockers Clopidogrel Diltiazem, Diuretics NSAIDS Simvastatin, Spironolactone, Statins Warfarin	NR
Stevenson et al. [39]	NR	NR	NR	NR
Ruiz et al. [40]	Any toxicity	52^	Carboplatin	100
	Any haematologic	35^	Paclitaxel	100
	Neutropenia	27^		
	Infection with neutropenia	4^		
	Anaemia	4^		
	Thrombocytopenia	4^		
	Any non-haematologic	21^		
	Fatigue	4^		
	Arthralgia	4^		
	Hyperglycaemia	4^		
	Infusion reaction	2^		
	Neuropathy	2^		
	Hyponatraemia	2^		
	Cardiac ischemia	2^		
	Death not otherwise specified	2^		

Table 5 (continued)

Study	Medication harm	Frequency of medication harm (%)	Medications/classes of medications involved	Frequency of medications/classes involved (%)
Schmader et al. [41]	Diarrhoea	8.9	Antimicrobial Blood modifiers Cardiovascular, Central nervous system Hormones	NR
	Renal insufficiency	7.2		
	Hypoglycaemia	5.7		
	Postural hypotension	4.4		
	Dizziness	2.9		
	Rash	2.5		
	Somnolence	2.2		
	Hypotension	2.1		
	Hyperkalaemia	1.6		
	Nausea	1.6		
	Others	60.9		
Hanlon et al. [42]	Bradycardia Cardiovascular, Constipation Diarrhoea, Dizziness, Dyspepsia Hypoglycaemia Kidney function abnormality Somnolence	NR	Anticoagulants	8.6
			Diuretics	8.5
			ACEI	6.2
			Antidiabetics	6.2
			Anticholinergics	6.2
			Anti-infectives	5.4
			NSAIDs	5.4
			Non-TCA	4.8
			Digoxin	4.4
			Beta blockers	4.2
			Calcium channel blocker	3.8
			Opioid analgesics	2.8
			Antiepileptic	2.4
			Others	33.8
Ekerstad et al. [43]	Abdominal pain Constipation Diarrhoea Fainting, Falling, Fever Gastrointestinal bleeding Nausea Palpitations Tiredness Vertigo	NR	Aspirin Carbamazepine, Citalopram, Clindamycin, Clopidogrel Digoxin, Duloxetine Felodipine Furosemide Metoprolol Oxycodone Spironolactone Warfarin	NR

Major bleeding Identified using the primary discharge diagnosis in the inpatient setting with an ICD-9-CM or ICD-10-CM diagnosis code or procedure code. The list of MB diagnosis codes was adapted from a validated administrative claim-based algorithm and the International Society on Thrombosis and Haemostasis's definition of MB. MB also included gastrointestinal (GI) bleeding, intracranial haemorrhage (ICH), and bleeding at other critical sites (e.g., liver, splenic, and ocular haemorrhage) using primary principal diagnosis. *Clinically relevant non-major bleeding* Identified using secondary diagnosis codes for bleeding at non-critical sites in the inpatient setting (not including patients with MB), or a diagnosis code in any position for GI bleeding or other bleeding in the ambulatory setting. *Recurrent VTE* Identified using a primary discharge diagnosis for VTE in the inpatient setting ≥7 days following the qualifying index VTE encounter. *Non-accidental falls* Identified based on patient's diagnosis in the hospital data using ICD-10 codes. Definition not formally defined in study. *Antimicrobial* Study did not report the definition. *Blood modifiers* Study did not report the definition. *Cardiovascular* Study did not report the definition. *Central nervous system* Study did not report the definition. *Hormones* Study did not report the definition

ACEI Angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor blockers, *ICD* International Classification of Disease, *ICH* intracranial haemorrhage, *MB* major bleeding, *NA* not applicable, *NR* not reported, *NSAIDS* nonsteroidal anti-inflammatory drugs, *OR* odds ratio, *TCA* tricyclic antidepressant, *VTE* venous thromboembolism

^Cycle 1 of chemotherapy with Grade 3–5 toxicity

4.5 Causality Analysis

Causality analysis is important in confirming a link between medications and potential patient harm [73]. In our scoping review, only five of nine studies [35, 39, 41–43] used a causality analysis tool to evaluate medication harm, and only one study [39] used the Naranjo algorithm coupled with clinical judgement by an independent panel (considered the gold standard) [74]. Studies that did not include causality analysis [36, 37] were limited in the accuracy of their outcome measurement, as an event may not be true medication harm. The three methods used to conduct a causality analysis included the Naranjo algorithm [55], Hallas criteria [56], and clinical judgement. Clinical judgement was used by one study [43] but when used alone this is a subjective method that can be confounded by assessor bias.

Whilst different causality assessment tools use similar criteria, their application and scoring systems differ (e.g., Naranjo is a score-based system with different cut-off points depending on ten criteria, whereas the Hallas has only five criteria applied using expert judgement). Limitations in causality analysis tools have been described by previous studies [73, 75]. Ideally, causality analysis should be undertaken using a validated tool coupled with clinical judgement [76]. Clinical judgement should be conducted with an experienced panel of clinicians that are multidisciplinary, and where inter-rater reliability is considered in evaluating assessor bias [77]. Studies should also establish standardised protocols, detailing the steps and assessors involved in rating events to ensure transparent reporting. In this review, only two studies [41, 42] reported using an expert panel coupled with a causality analysis tool.

4.6 Polypharmacy and Frailty

Polypharmacy is known to increase an individual's risk of medication harm [78–80]. Similarly, frailty also appears to be associated with an increased risk of medication harm [39, 81]. Polypharmacy, frailty, and medication harm are intertwined constructs. Therefore, we need adequately sized and robust studies that have investigated medication harm and made the statistical adjustment to eliminate the potential confounding effects of polypharmacy. In this review, only Stevenson et al. [39] demonstrated an independent relationship with medication harm, with frail individuals being ten times more likely to experience medication harm. Further research is needed to confirm this association.

4.7 Future Research

Rigorous prospective studies that comprehensively evaluate medication harm in sufficiently powered studies with groups of frail and non-frail patients, using a broad range of medications likely to be representative of the population as a whole, are needed to determine if frailty is an independent predictor of medication-related harm. Studies could further examine and classify medications/medication classes most associated with ADRs, especially in the frail population. The identification of high-risk medications could serve as a useful tool to guide prescribing decisions.

5 Conclusion

Our scoping review identified and appraised nine studies that evaluated the relationship between frailty and medication harm. In the six studies comparing frail versus non-frail cohorts, frail individuals were reported to have a higher incidence of medication harm, harm-related hospitalisation, and mortality, and these risks were magnified if patients were receiving CNS-acting medications or warfarin. When evaluating the association between frailty and medication harm, only one study identified a relationship independent of polypharmacy.

With continued research in this field, frailty screening tools could be evaluated as part of pharmacist interventions to inform the risk of medication harm in individuals. However, studies need to be comprehensive in their evaluation to encompass the types of medicines involved, the definition of harm, and other key measures such as severity and preventability of medication harm.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40266-022-00940-3.

Acknowledgements The authors would like to thank the Princess Alexandra Research Foundation for their generous support that allowed the time to conduct research in the field of patient safety. We are also sincerely thankful to Mrs Christine Dalais, our liaison librarian at The University of Queensland, who provided guidance and assisted with the literature search.

Funding Open Access funding enabled and organized by CAUL and its Member Institutions.

Declarations

Ethics declaration Not applicable.

Funding By Princess Alexandra Research Foundation.

Authorship and conflict of interest The authors have no conflicts of interest to declare.

Ethics approval Not applicable.

Consent to participate and consent to publish Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Author contributions JL, MB, DL, NF designed and conducted the study. Data collection and analysis were undertaken by JL, MB, DL, NF, LH. The first draft of the manuscript was written by JL, MB, NF, and all authors commented on previous versions of the manuscript. All authors revised the article and approved the final manuscript.

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