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SYSTEMATIC REVIEW AND META-ANALYSIS

# Potentially inappropriate prescribing and its associations with health-related and system-related outcomes in hospitalised older adults: A systematic review and meta-analysis

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**Aims:** To synthesise associations of potentially inappropriate prescribing (PIP) with health-related and system-related outcomes in inpatient hospital settings.

**Methods:** Six electronic databases were searched: Medline Complete, EMBASE, CINAHL, PyscInfo, IPA and Cochrane library. Studies published between 1 January 1991 and 31 January 2021 investigating associations between PIP and health-related and system-related outcomes of older adults in hospital settings, were included. A random effects model was employed using the generic inverse variance method to pool risk estimates.

**Results:** Overall, 63 studies were included. Pooled risk estimates did not show a significant association with all-cause mortality (adjusted odds ratio [AOR] 1.10, 95% confidence interval [CI] 0.90–1.36; adjusted hazard ratio 1.02, 83% CI 0.90–1.16), and hospital readmission (AOR 1.11, 95% CI 0.76–1.63; adjusted hazard ratio 1.02, 95% CI 0.89–1.18). PIP was associated with 91%, 60% and 26% increased odds of adverse drug event-related hospital admissions (AOR 1.91, 95% CI 1.21–3.01), functional decline (AOR 1.60, 95% CI 1.28–2.01), and adverse drug reactions and adverse drug events (AOR 1.26, 95% CI 1.11–1.43), respectively. PIP was associated with falls (2/2 studies). The impact of PIP on emergency department visits, length of stay, and health-related quality of life was inconclusive. Economic cost of PIP reported in 3 studies, comprised various cost estimation methods.

**Conclusions:** PIP was significantly associated with a range of health-related and system-related outcomes. It is important to optimise older adults' prescriptions to facilitate improved outcomes of care.

KEYWORDS
Beers criteria, inappropriate medication, inappropriate prescribing, medication therapy management, prescribing omissions, STOPP/START

## 1 | INTRODUCTION

The world's population is aging, with recent statistics showing that older people make up a considerable proportion of the world's population. In 2017, 1 in 8 people worldwide was aged 60 years or older and it is expected that this proportion will increase to 20% by 2050.[1] This demographic transition has a number of implications to healthcare. Older adults are prone to multiple chronic

conditions,[2] necessitating the use of multiple medications, or polypharmacy.[3,4]

Polypharmacy, commonly defined as the concurrent use of 5 or more regular medications,[4,5] is increasingly prevalent as the population ages. A recent population-based study estimated the prevalence of polypharmacy among older Australians is high (36%), with the oldest old (aged 85 years or older), the most affected.[6] The rate of polypharmacy is even higher in hospitalised patients (76%).[7]

The use of polypharmacy may be clinically justifiable, but it is important to identify patients with inappropriate polypharmacy that may lead to adverse clinical outcomes.[3] Older adults are particularly vulnerable to the negative impact of polypharmacy due to age-related physiological changes that affect the pharmacokinetics and pharmacodynamics of medications,[8] and their under-representation in clinical trials, resulting in a lack of benefit/risk data.[9] This vulnerability makes safe and effective prescribing a challenging and complex process in older adults,[8] contributing to an increased risk of potentially inappropriate prescribing (PIP).

PIP involves prescribing medications that may not produce benefits relative to harm, or not prescribing medications that are recommended, which may pose significant harm to older adults.[8] PIP encompasses potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs).[10] PIMs are medications with a greater risk than benefit to a patient while PPOs are failures to prescribe medications of potential benefit.[10,11]

Numerous tools are available in the literature to identify PIPs.[12] These tools can be grouped into implicit (judgement-based) and explicit (criterion-based) tools, or a combination of both approaches.[8,12] Explicit tools can be easily applied with little or no clinical judgement, and the most studied explicit tool is the Beers list, which was first published in the USA in 1991[13] and last updated in 2019.[14] Other explicit tools, the STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) criteria, were developed in Europe in 2008 (later revised in 2014),[10,15] and have now become widely used tool in Europe and elsewhere.[16–19] The Beers and STOPP criteria address PIMs, whereas the START criteria enable detection of PPOs.

The link between polypharmacy and PIP is well established.[19–23] As with polypharmacy, PIP is common in older adults[19] and is associated with an increased use of healthcare resources and medication costs.[23,24] Previous systematic reviews have identified some links between PIPs and adverse drug events (ADEs) and hospitalisation, but are inconclusive on other outcomes such as mortality, emergency department (ED) visits and medication-related hospital readmissions.[25–29] These reviews have predominantly focused on studies using a limited number of tools, such as the Beers and STOPP criteria. It has not yet been established whether failure to prescribe medications of potential benefit, comprising PPOs, has clinical and resource implications. Also, this evidence has most often originated from either population-based studies or analyses involving long-term care residents, with limited data available from populations of older hospitalised patients. Moreover, the full range of outcomes associated with PIPs is not well established, especially in hospital settings. It is unclear whether prescribing of PIPs during inpatient care is associated with health-related outcomes, such as ADEs and quality of life or with system-related outcomes, such as mortality and hospital readmission. Thus, the aim of this systematic review was to synthesise the available literature on the associations of PIP in the inpatient hospital setting, identified through any validated and published tool, with health-related and system-related outcomes.

## 2 | METHODS

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[30] and the study protocol was registered on PROSPERO (CRD42020182598).

### 2.1 | Data sources and search strategy

A comprehensive electronic search of the medication safety literature was undertaken using the following databases: Medline Complete (1916); EMBASE (1947); Cumulative Index to Nursing and Allied Health Literature (CINAHL) Complete (1937); PyscInfo (1806); Cochrane Central Register of Controlled Trials (1996); and International Pharmaceutical Abstracts (IPA; 1970) databases. The searches were limited to English language papers published between 1 January 1991 and 31 January 2021; the start date coincided with the first validated list of PIMs published in 1991.[13] The search terms included synonyms related to inappropriate prescribing, older populations, hospital care, and health-related and system-related outcomes. These keywords were hand-picked from the literature during preliminary literature searching. The key concepts were searched line by line and then combined using Boolean operators (OR, AND) to identify eligible studies. Keywords were customised to database-specific Medical Subject Headings (MeSH) and indexing terms to capture relevant studies. In addition to language and year of publication, the database searches were also limited to studies with abstracts, and conducted on humans (Appendix 1). The university research librarian provided advice about setting up and conducting the search strategies for the various library databases.

In addition to electronic database searches, reference lists of relevant reviews and included articles were examined manually to identify any additional eligible studies. Search results were then imported into an EndNote library to manage article collections and remove any duplicate studies. The de-duplicated search results were transferred to Covidence for independent blind screening of relevant papers.

### 2.2 | Eligibility criteria and study selection

For inclusion in this review, older adults aged 65 years (60 years for low-and middle-income countries[31]) or older, who were admitted to hospital for inpatient services, irrespective of the types of admissions

and ward specialities, were considered. Studies that involved multiple healthcare settings were required to clearly report separate data for each hospital setting. All observational cohort studies, cross-sectional studies and case–control studies investigating the association between PIPs and health-related outcomes were included. To be included, studies were required to employ validated criteria to identify PIPs,[12] such as the Beers, STOPP and START criteria. Studies that employed modified versions of validated tools, and country-specific tools were also considered. However, studies must have employed the tools in their entirety, and not been limited to specific medications or disease conditions.[25,26,28]

The primary outcomes of interest were health-related, such as rates of adverse drug reactions (ADRs) and system-related (e.g. all-cause mortality, ED visits, hospital readmissions, length of stay). These outcomes could be measured across any period—before, during or after hospital discharge. However, studies that only measured PIP as an outcome (e.g. the impact of hospitalisation on the incidence of PIP) were not included. Secondary outcomes included health-related quality of life, falls, functional decline, and cost-related to PIPs. Similarly, these secondary outcomes could be measured any time, and data were extracted on these outcomes without any preset definitions, and hence, we adopted the definitions employed by each study.

Review articles, qualitative studies, conference abstracts without full-text publications, case reports, editorials and commentaries were excluded. Studies that did not address outcomes of inappropriate medication use, including those exploring the prevalence of PIP per se, and risk factors for PIPs were also excluded.

Studies retrieved from all the databases and those located from the additional sources were screened independently by 2 reviewers (A.M., B.R./E.M.) for inclusion. Any discrepancies at the title and abstract level were resolved by a third reviewer (B.R./E.M.). Pilot testing on an initial sample of 15 studies demonstrated only moderate agreement between 2 independent reviewers (A.M., B.R.) in title and abstract screening (Cohen's $\kappa = 0.47$; % agreement = 73%). Further discussion resulted in additional detail in the eligibility criteria to improve agreement between reviewers. Studies deemed eligible after title and abstract screening passed into full text review. The full texts of potentially eligible studies were retrieved and assessed independently by 2 reviewers (A.M., B.R./E.M.) against the inclusion criteria, and ineligible papers were discarded. Any discrepancies at the full text level were again resolved by a third reviewer (B.R./E.M.).

## 2.3 | Data extraction

A standardised, prepiloted document was employed for data extraction and quality assessment of the included studies. Items in the data extraction tool included general study characteristics (e.g. study authors, country of origin, study design, characteristics of the population), tools used to identify PIPs, medications associated with PIPs, and main results on health-related outcomes due to PIP.

## 2.4 | Quality assessment

As we proposed to include diverse study designs, we employed the Mixed Methods Appraisal Tool (MMAT v2018) for assessment of study quality.[32] The MMAT was adopted for quality assessment of quantitative nonrandomised studies, which includes cohort, case–control and cross-sectional analytic studies. In line with our study objectives, we set out a priori to consider only the control arm of interventional studies for quality assessment, using the same methodological criteria as the quantitative nonrandomised study designs.

## 2.5 | Data analysis

Descriptive analysis was conducted on extracted data from all included studies. A meta-analysis was conducted if 2 or more studies reported data suitable for quantitative synthesis. Health-related or system-related outcomes were pooled as an odds ratio (OR) or hazard ratio (HR) together with a 95% confidence interval (95% CI) using a random-effects model with the generic inverse variance method. Meta-analysis was performed for both crude and adjusted risk estimates. For studies that contributed 2 or more risk estimates for the same outcome, sensitivity analysis was conducted by selecting only the weakest association. We also conducted subgroup analyses based on various factors, such as the tool used to identify PIPs, study design and location, and quality score. All meta-analyses were performed with Review Manager (RevMan) software (RevMan V.5.3, The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Pooled prevalence estimates were carried out using OpenMeta[Analyst] (http://www.cebm.brown.edu/openmeta/).

# 3 | RESULTS

The database searches yielded 1821 results. After removal of duplicates, titles and abstracts of 1282 unique articles were independently screened, with 1116 excluded. The full texts of the remaining 166 studies were reviewed in detail using inclusion and exclusion criteria. Of these, 103 articles were excluded, mainly because studies reported a different outcome of interest ($n = 58$). The final screening identified 63 studies[33–95] suitable for inclusion in this review (Figure 1).

## 3.1 | Characteristics of included studies

The included studies were conducted in 21 different countries (Table 1): 32 (52%) studies were performed in Europe, 13 (22%) in North America, 11 (14%) in Asia, 4 (7%) in Australia and 3 (5%) in Brazil, with publication dates between 2005 and 2020. Forty-seven studies were cohort studies (25 were conducted prospectively), and 11 were cross-sectional studies. The remaining studies were case–

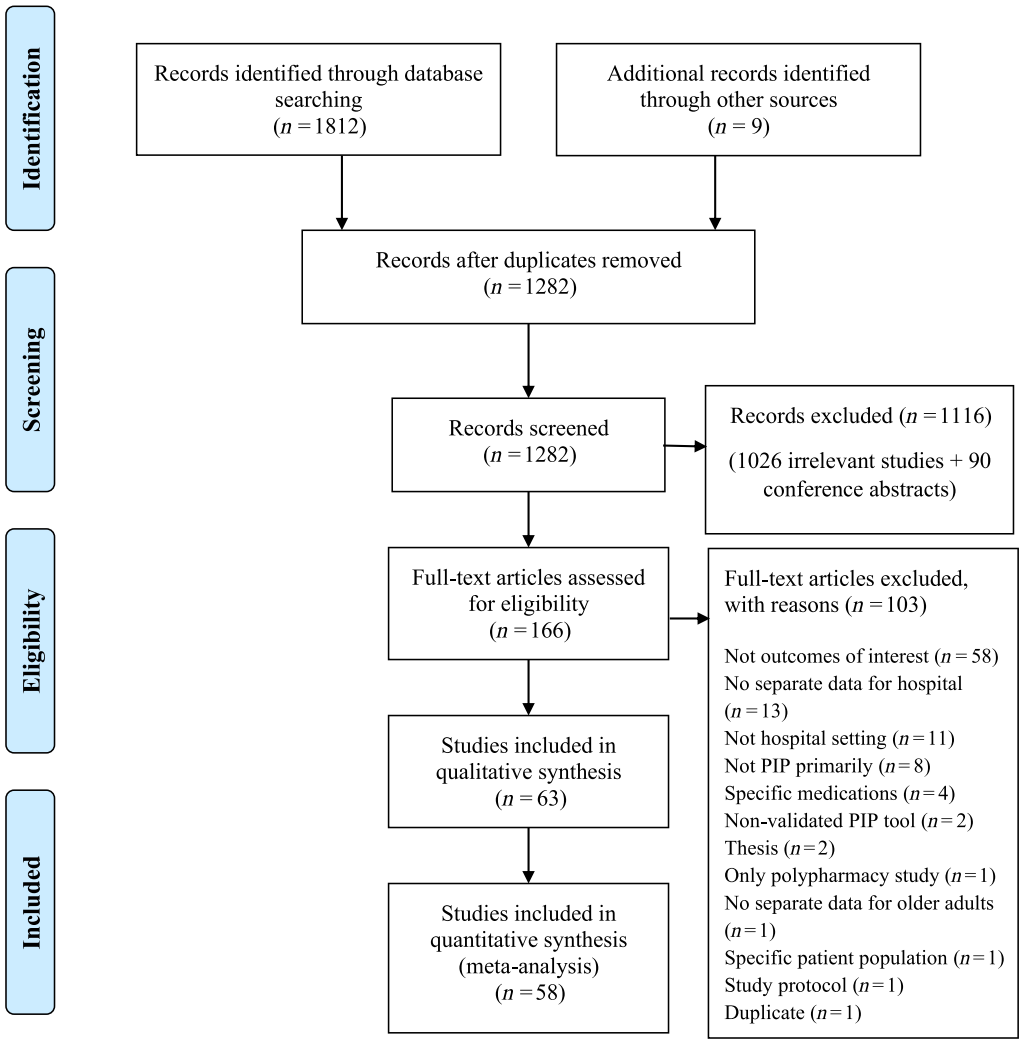


**FIGURE 1** Flow diagram of the selection process

control or comparative retrospective (3 studies), mixed-methods (involving a retrospective clinical audit) and a secondary analysis of a randomised controlled trial (each 1 study). Most studies ($n = 44$) were confined to single centres, mainly in geriatric or medical hospital wards. Sample sizes for included studies ranged from 52 to 45 809 individuals. The reported mean and median ages of participants in included studies ranged from 72.4–88.3 and 71–88 years, respectively. The average percentage of male participants among the included studies was 45%.

Over half of the studies ($n = 36$) assessed PIP exposure using any versions of the Beers criteria, followed by STOPP (26 studies) and START criteria (12 studies). Other tools employed to assess the appropriateness of medication use included Medication Appropriateness Index (3 studies), PRISCUS list and STOPP Frail (each 1 study) and other study or country specific tools (8 studies). Study or country specific tools were derived mainly from a mix of tools, such as the Beers and STOPP criteria. Medical record review, either paper or electronic, was the main source of data for PIP identification. Some studies followed-up patients for assessment of outcomes, ranging from 3 weeks to 49 months (Table 1). Based on the MMAT, 42 studies fulfilled at least 4 of the 5 items (Appendix 2).

## 3.2 | PIP prevalence and common medications involved in PIPs

Based on different sets of PIP criteria, more than 1 prevalence estimate was reported in 25 studies, and discrete prevalence estimates for care transitions (e.g. admission, discharge) per study were reported in 8 studies. Overall, the pooled PIM prevalence was estimated at 47% (95% CI 37–56), 46% (95% CI 39–53), and 56% (95% CI 40–72) according to the different versions of Beers, STOPP and study or country-specific criteria, respectively. The overall estimated PPO prevalence, from the pooled analysis of the START criteria, was 55% (95% CI 46–64) (Appendix 3). The most frequently reported PIMs or medication classes were benzodiazepines, antipsychotics, antihistamines/anticholinergics and antithrombotics, whereas the most frequently reported PPOs were: antiplatelet therapy with documented

**TABLE 1** Characteristics of included studies ($n = 63$)

| Authors, year | Country | Study design | Study setting, specialty | Sample size | % male | Age (y), mean (SD) | Study period, follow–up duration (mo) | PIP tool | Data source of PIP | Outcomes assessed | PIP prevalence, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Akkawi *et al.* 2019[33] | Malaysia | C | Single centre, medical & surgical wards | 502 | 51.4 | 72.4 (5.9) | Apr–Oct 2016 & Apr–Oct 2017, NR | STOPP/START v2 | Medical record | HRQoL | STOPP v2: 28.5; START v2: 45.6; STOPP/START v2: 59.2 |
| Bachmann *et al.* 2018[34] | Switzerland | PC | Single centre, geriatric inpatient rehabilitation | 210 | 53.8 | 75.5 | Feb–Nov 2014, 0.75 | STOPP 2008 | Referral letter | HRQoL, mobility | 43.3 |
| Basnet *et al.* 2018[35] | USA | RC | Multicentre, medical & surgical units | 24 204 | 45 | 78 (9) | Sep 2011–Dec 2013, 1 | Beers 2012 | Electronic medical record | HR | 58.9 |
| Bo *et al.* 2018[36] | Italy | PC | Multicentre, internal medicine & geriatric wards | 1000 | 45.5 | 81.9 (7.7) | Dec 2015–Jun 2016, 6 | Beers 2015 | Medical record, patient interview | M, HR | 63 |
| Brunetti *et al.* 2019[37] | Italy | PC | Multicentre, geriatric & internal medicine wards | 611 | 51.6 | 81.6 (7.0) | Mar–June 2017, 6 | STOPP/START v2 | NS | M, HR | STOPP v2:54.8; START v2: 47.3; STOPP/START v2: 71.7 |
| Cabré *et al.* 2018[38] | Spain | C | Single centre, acute geriatric unit | 3292 | 39.9 | 84.7 (6.6) | Jan 2001–Dec 2010, NR | Beers 1991, STOPP v1 | Medical record | ARA | STOPP v1: 20; Beers 1991: 9 |
| Cheong *et al.* 2019[39] | UK | CC | Single centre, NR | 200 | 34.5 | 83.8 (5.68) | Jan–Dec 2015, NR | Beers 2015 | Electronic discharge summary record | HR | 33 |
| Corsonello *et al.* 2009[40] | Italy | PC | Multicentre, acute care medical wards | 506 | 45.7 | 80.1 (6.0) | Apr– Jun 2007, 12 | Beers 2003 | Medical and nurse records | FD, ADE | Admission: 20.6; during hospital stay: 9.7 |

**TABLE 1** (Continued)

| Authors, year | Country | Study design | Study setting, specialty | Sample size | % male | Age (y), mean (SD) | Study period, follow-up duration (mo) | PIP tool | Data source of PIP | Outcomes assessed | PIP prevalence, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Counter *et al.* 2018[41] | UK | RC | Single centre, general medical unit | 259 | 49 | 77 | Nov 2013–Jun 2014, 41.5 | STOPP/START v2 | Inpatient clinical notes, electronic records of outpatient clinic review, GP referral & discharge letters | HR, M | STOPP v2: 59.1; START v2: 69.1; STOPP/START v2: 83.8 |
| Dalleur *et al.* 2012[42] | Belgium | C | Single centre, NR | 302 | 37.4 | Median (IQR): 84 (81–88) | Dec 2007–Nov 2008, 12 | STOPP/START v1 | Electronic medical record | ARA | STOPP v1: 47.7; START v1: 62.9 |
| De Vincentis *et al.* 2020[43] | Italy | PC | Multicentre, medical wards | 2631 | 48.6 | Median: 79.6 | 2010–2016, 3 | Beers 2019, STOPP 2015 | REPOSI registry | M, HR, FD | Beers 2019: 31.1; STOPP v2: 25.6 |
| Eshetie *et al.* 2020[44] | Australia | PC | Multicentre, general medicine wards | 181 | 45.3 | Median: 87.5 | 5 Jun–7 Jul 2017, 1.25 | STOPP 2015, Beers 2019 | Medical record | ARA | People with dementia: Beers [A: 79.1, D: 84.6]; STOPP [A: 78, D: 79.1]; people without dementia: Beers [A: 81.1, D: 85.6]: STOPP [A: 87.8, D: 85.6] |
| Fabbietti *et al.* 2018[45] | Italy | PC | Multicentre, acute care wards of geriatric medicine | 647 | 51 | 80.1 (6.9) | Jan–Dec 2013, 12 | STOPP 2015, Beers 2015 | MEDELNET-AC project | HR | STOPP v2: 30; Beers 2015: 27.7 |
| Fabbietti *et al.* 2018[46] | Italy | PC | Multicentre, geriatric and internal medicine acute care wards | 733 | 45.2 | 80.06 (7.01) | Jun 2010–May 2011, 3 | STOPP 2015, Beers 2015 | CRIME project | FD | STOPP v2: 40.2; Beers 2015: 35.9 |

(Continues)

**TABLE 1** (Continued)

| Authors, year | Country | Study design | Study setting, specialty | Sample size | % male | Age (y), mean (SD) | Study period, follow-up duration (mo) | PIP tool | Data source of PIP | Outcomes assessed | PIP prevalence, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Fahrni *et al.* 2019[47] | Malaysia | PC | Multicentre, general medical or surgical services | 301 | 54.8 | Median (IQR): 72 (67–77) | Jun–Dec 2014, 7 | STOPP START v1 | Medical record | ADE, ARA | STOPP v1: 34.9; START v1: 37.9; STOPP/START v1: 58.5 |
| Floroff *et al.* 2014[48] | USA | RC | Singe centre, neuroscience IcU | 112 | 45.5 | 65–74 y: 36.6%; 75–84 y: 36.6%; ≥85 y:26.8% | Mar–Jul 2011, 5 | Study specific tool | Electronic medical record | LoS, M, time to recovery | 81.3 |
| Forget *et al.* 2020[49] | Canada | RC | Single centre, preoperative clinic | 252 | 46 | Median (IQR): 72 (69–76) | Jan 2017–Jan 2018, 3 | MedSafer | Community pharmacy | ED visit, LoS | 78 |
| Fromm *et al.* 2013[50] | Germany | RC | Multicentre, geriatric units | 45 809 | 30.8 | Median (IQR): 82 (78–86) | Jan 2009–Dec 2010, 24 | PRISCUS list | Geriatrics in Bavaria databank | FD | 25.9 |
| Gallagher *et al.* 2008[51] | Ireland | PC | Single centre, medical and surgical services | 715 | 46 | Median (IQR): 77 (72–82) | 2007, 4 | STOPP v1, Beers 2003 | Medical record, GP referral letter, patient, pharmacist | ARA | STOPP v1: 35; Beers 2003: 25 |
| Gallagher *et al.* 2008[52] | Ireland | PC | Single centre, medical & surgical services | 597 | 46 | 77 (7) | NR, 3 | Beers 2003 | Medical record, GP referral letter, GP, pharmacy | ARA | 32 |
| Galli *et al.* 2016[53] | Brazil | C | Single centre, medical or cardiovascular ICU | 599 | 54.9 | Median (IQR): 71 (65–77) | Jan–Dec 2013, NR | Beers 2012 | Medical record | ADR | 98.2 |
| Gillespie *et al.* 2013[54] | Sweden | RCT | Single centre, internal medicine wards | 368 | 41.3 | 86.7 (4.1) | Oct 2005–Jun 2006, 12 | MAI, STOPP START v1 | Electronic case notes | HR, ARA | NR |
| Glans *et al.* 2020[55] | Sweden | CR | Single centre, NR | 720 | 49.5 | Case: 80 (8); control: 78 (8) | 2017, 1 | SNBHW criteria | Electronic medical record | HR | NR |
| Gosch *et al.* 2014[56] | Austria | RC | Single centre, geriatrics and internal medicine | 457 | 17.5 | 80.61 (7.07) | 2000–2004, 38 | STOPP START v1 | Discharge summary | M | STOPP v1: 53.4; START v1: 79.9; STOPP/START v1: 90.4 |

**TABLE 1** (Continued)

| Authors, year | Country | Study design | Study setting, specialty | Sample size | % male | Age (y), mean (SD) | Study period, follow-up duration (mo) | PIP tool | Data source of PIP | Outcomes assessed | PIP prevalence, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gutiérrez-Valencia *et al.* 2017[57] | Spain | RC | Single centre, acute geriatric unit | 200 | 35 | 88.3 (5.7) | Jan–Feb 2015, 6 | Beers 2015, STOPP/START v2 | Medical record, discharge summary | HR, M, ED visit | STOPP v2 [A: 68.5; D: 71.5]; START v2 [A: 58; D: 58]; Beers 2015: [A: 71; D: 71.5] |
| Hagstrom *et al.* 2015[58] | USA | PC | Single centre, NR | 560 | 53 | NR | May 2012–Apr 2013, NR | Beers 2012 | NR | LoS, HR, cost | 67.8 |
| Hamilton *et al.* 2011[59] | Ireland | PC | Single centre, medical and surgical services | 600 | 40.2 | Median (IQR): 77 (72–83) | NR, 4 | Beers 2003, STOPP v1 | Medical record, patient/care giver interviews | ADE | STOPP v1: 56.2; Beers 2003: 28.8 |
| Hattori *et al.* 2020[60] | Japan | RC | Signe centre, geriatric hospital | 116 | 42.2 | 85.3 ± 10.2 | 2016–2018, 24 | START v2 | Electronic medical record | M | 53.3 |
| Iaboni *et al.* 2017[61] | USA | PC | Multicentre, NR | 477 | 24.5 | User: 78.5 (8.4); nonuser: 78.4 (9.1) | 2008–2012, 12 | Beers 2012 | Medication record | Time to functional recovery | 51 |
| Jensen *et al.* 2014[62] | Denmark | PC | Single centre, acute medical unit | 71 | 55.00 | Median: 78.7 | Oct–Dec 2011, 1 | Red–yellow–Green list (Danish criteria) | Personal electronic medication record, patient interview/care giver interview | HRQoL, FD | 84.5 |
| Kanaan *et al.* 2013[63] | USA | PC | Multicentre, NR | 731 | 48.4 | 78.8 (7.1) | Aug–Dec 2010, 1.5 | Beers 2012 | Medical record | ADE | NR |
| Kersten *et al.* 2015[64] | Norway | RC | Single centre, medical and geriatric wards | 232 | 40.9 | 86 (5.7) | 2012, 8 | Study specific tool | Medical record, GP referral letter | LoS, FD | Admission: 39.2; discharge: 37.9 |
| Komagamine *et al.* 2019[65] | Japan | PC | Single centre, internal medicine ward | 739 | 47.4 | Median (IQR): 82 (74–88) | May 2017–Nov 2018, 1 | Beers 2015 | Electronic medical record | HR | Admission: 47.2; discharge: 32.2 |
| Kose *et al.* 2020[66] | Japan | RC | Single centre, rehabilitation ward | 569 | 33.6 | Median (IQR) 79 (73–85) | July 2010–October 2018, NR | Beers 2019 | Medical record | FD | NR |
| Laroche *et al.* 2006[67] | France | PC | Single centre, acute medical geriatric unit | 2018 | 30.6 | 85.2 (6.6) | Jan 1994–Apr 1996; May 1997–Jan 1999; 49 | Beers 1997 | Prescription, patient/care giver interview, GPs | ADR | 66 |

(Continues)

**TABLE 1** (Continued)

| Authors, year | Country | Study design | Study setting, specialty | Sample size | % male | Age (y), mean (SD) | Study period, follow-up duration (mo) | PIP tool | Data source of PIP | Outcomes assessed | PIP prevalence, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Lau *et al.* 2017[68] | China | RC | Singe centre, medical wards | 165 | 39.4 | 83.35 (5.49) | 1–31 May 2016, 1 | STOPP v2 | Medical record | HR | 27.3 |
| Lester *et al.* 2019[69] | Canada | C | Single centre, level 1 trauma centre | 319 | 64.9 | 76 | Jan 2013–Dec 2014, 1 | Beers 2015 | Medical record | M, LoS | 63.9 |
| Manias *et al.* 2015[70] | Australia | RC | Single centre, medical ward | 200 | 42.5 | 81.4 (7.16) | May 2012–April 2013, NR | STOPP START v1 | Medical record | ADE | STOPP: 51; START: 74 |
| Manias *et al.* 2019[71] | Australia | MM | Single centre, ED and general medical units | 249 | 38.6 | Median (IQR): 88 (86–91) | Jan–Dec 2016, NR | STOPP START v2 | Medical record | ADE | PIMs (ED: 51; T1: 37.1; T2: 40.4; D: 36.9); PPOs (ED: 44.6; T1:43.8; T2:41.8; D: 36.9) |
| Mansur *et al.* 2009[72] | Israel | PC & RC | Single centre, acute geriatric ward | 212 | 38.2 | 81.1 (7.25) | Jul 2004–Jun 2005, 3 | Beers 2003 | Medical record | HR, M | A: 43.5; D: 44.4 |
| Nagai *et al.* 2020[73] | Japan | RC | Multicentre, surgical ward | 253 | 13.4 | 75.6 (8.6) | Oct 2014–Dec 2018, 12 | STOPP-J | Electronic medical record | F, FD | 42.3 |
| Ni Chroinin *et al.* 2016[74] | Australia | RC | Single centre, medical & surgical wards | 534 | 51.7 | 78 (9) | Jan 2013, 1 | STOPP v1 | Medical record | ARA | [A: 54.8, D: 60.8] |
| Olsson *et al.* 2011[75] | Sweden | PC | Singe centre, NR | 140 | 37.9 | 83.4 (5.0) | Sep 2006–May 2007, 12 | MAI | Medical record, prescription, medication lists | HRQoL | Mean MAI score: 61.3 |
| O'Connor *et al.* 2012[76] | Ireland | PC | Single centre, medical & surgical services | 513 | 44 | Median (IQR): 77 (72–82) | Jul–Oct 2010,4 | STOPP v1 | NR | ADR | 51 |
| Onder *et al.* 2005[77] | Italy | RC | Multicentre, NR | 5152 | 47.8 | 78.8 (8.4) | 1997–1998, 24 | Beers 2003 | GIFA database | M, LoS, ADR | 28.6 |
| Ozalas *et al.* 2017[78] | USA | RC | Single centre, acute care for elders unit | 340 | 41.8 | 84 (11) | Jan–May 2011, NR | Beers 2003 & 2012 | Medical record | M, LoS, ADE | Beers 2003: 42.1; Beers 2012: 67.4 |
| Page *et al.* 2006[79] | USA | RC | Single centre, internal medicine services | 389 | 31.1 | 79 | Mar 2000–Aug 2001, 18 | Beers 2003 | Medical record | M, ADE, LoS | 27.5 |

**TABLE 1** (Continued)

| Authors, year | Country | Study design | Study setting, specialty | Sample size | % male | Age (y), mean (SD) | Study period, follow-up duration (mo) | PIP tool | Data source of PIP | Outcomes assessed | PIP prevalence, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pardo-Cabello *et al.* 2017[80] | Spain | C | Single centre, internal medicine unit | 275 | 43.6 | Median (IQR): 82 (76–86) | Feb–Apr 2016, NR | STOPP 2 | Medical record, discharge summary | Cost | 41.5 |
| Parekh *et al.* 2018[81] | UK | PC | Multicentre, medical wards | 1280 | 42 | Median (IQR): 82 (75–87) | 2013–2015, 12 | Beers 2015 | PRIME study | HR, M, ADR, ARA | 21.6 |
| Pasina *et al.* 2014[82] | Italy | C | Multicentre, internal medicine & geriatric wards | 844 | 48.8 | 78.8 (7.4) | 2008–2010, 3 | Beers 2003, 2012 | REPOSI registry | HR, M, ADE | Beers 2003: 20.1; Beers 2012: 23.5 |
| [a]Passarelli *et al.* 2005[83] | Brazil | PC | Single centre, internal medicine service | 186 | 38.7 | 73.6 (9.1) | Sep 2002–May 2004, NR | Beers 2003 | Medical record, patient interview | ADR | 67.4 |
| Rahman *et al.* 2019[84] | USA | RC | Single centre, medical ICU | 346 | 56.4 | 65–74 y: 51.7%; ≥ 75: 48.3% | Jan–Dec 2014, 12 | Beers 2012, 2015, STOPP v1 | Medical record | HR, M, LoS | STOPP v1 [A: 44.5, D: 42.9]; Beers 2012 [A: 58.1, D: 63.6], Beers 2015 [A: 68.5, D: 77.4] |
| Sevilla-Sanchez *et al.* 2017[85] | Spain | C | Single centre, acute care geriatric unit | 235 | 34.5 | 86.80 (5.37) | Nov 2014–Aug 2015, 10 | MAI, STOPP v2 | Patient-centred prescription | M, LoS | STOPP v2: 88.5; MAI: 97.4 |
| Sevilla-Sánchez *et al.* 2018[86] | Spain | C | Single centre, acute geriatric unit | 235 | 34.5 | 86.80 (5.37) | Nov 2014–Aug 2015, 10 | STOPP frail | Patient-centred prescription | M, ADE, ARA, LoS | 67.2 |
| Slaney *et al.* 2015[87] | Canada | RC | Single centre, alternate level of care | 52 | 58 | 82.69 (8.03) | Sep 2012, NR | Beers 2012 | Electronic medical record | ADE | 92 |
| [b]Tachi *et al.* 2019[88] | Japan | RC | Single centre, NR | 1236 | BCJV: 60.3; GM2015: 59.2 | BCJV: 77.9 (6.8); GM2015:77.7 (7.2) | Oct–Nov 2014, NR | BCJV, GL2015 | Electronic medical record | ADR, cost | BCJV: 24; GL2015: 72.4 |
| Tosato *et al.* 2014[89] | Italy | PC | Multicentre, geriatric & internal medicine | 871 | 46.8 | 80.2 (7) | Jun 2010–May 2011, NR | Beers 2012, STOPP v1 | CRIME project | ADR, FD | STOPP v1: 50.4; Beers 2012: 58.4; Combination: 75 |

(Continues)

**TABLE 1** (Continued)

| Authors, year | Country | Study design | Study setting, specialty | Sample size | % male | Age (y), mean (SD) | Study period, follow–up duration (mo) | PIP tool | Data source of PIP | Outcomes assessed | PIP prevalence, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| van der Stelt *et al.* 2016[90] | Netherlands | CC | Multicentre, NR | 338 | 47.3 | Cases: 79.4; control: 78.5 | Sep 2005–Jun 2006, 2 | Beers 2012; STOPP/START V1 | HARM study | ARA | STOPP v1: 34.1; START v1: 57.7; STOPP/START v1: 68.9; Beers 2012: 44.4 |
| Varallo *et al.* 2011[91] | Brazil | C | Single centre, internal medicine ward | 308 | NR | NR | Aug–Dec 2008, NR | Beers 2003 | Medical record, patient/care giver interview | ARA | 19.1 |
| Walker *et al.* 2019[92] | USA | RC | Single centre, level 1 trauma centre | 2181 | 48 | 78.5 | Jan 2014–Aug 2017, NR | Modified Beers criteria | Electronic medical record | F | 71.2 |
| Wang *et al.* 2019[93] | China | PC | Single centre, comprehensive department | 508 | 61.40 | 84.2 (5.9) | Jun 2015–Dec 2017, 36 | Beers 2015, Chinese criteria 2017 | NR | HR, M | Beers 2015: 69.3; Chinese criteria: 66.7 |
| Weir *et al.* 2020[94] | Canada | PC | Multicentre, internal medicine, cardiac & thoracic surgery wards | 2402 | 57.5 | Median (IQR): 76 [70–82] | Oct 2014–Nov 2016, 1 | Study specific tool | Pharmacy claims database, medical record | ADE, composite outcome | 66 |
| Zhang *et al.* 2017[95] | China | C | Single centre, geriatrics department | 456 | 73.20 | 81.8 (7.8) | May–Dec 2015, NR | Beers 2015, Beers 2012 | Medical record | ADR | Beers 2012: 44.7; Beers 2015: 53.5 |

A, admission; ADE, adverse drug event; ADR, adverse drug reaction; ARA, adverse drug reaction/event related hospital admission; BCJV, Beers Criteria–Japanese Version; CR, Comparative retrospective; CRIME, CRIteria to Assess Appropriate Medication Use among Elderly Complex Patients; D, discharge; ED, emergency department; HR, hospital readmission; M, mortality; FD, functional decline; F, falls; C, cross sectional; CC, case–control; RC, retrospective cohort; RCT, randomised controlled trials; PC, prospective cohort; GL2015, Guidelines for Medical Treatment and its Safety in the Elderly 2015; HARM, hospital admissions related to medication; HRQoL, health-related quality of life; LoS, length of stay; NR, not reported; PIP, potentially inappropriate prescribing; IQR, interquartile range; SD, standard deviation; STOPP, Screening Tool of Older Person's Prescriptions; STOPP-J, Screening Tool for Older Persons' Appropriate Prescriptions for Japanese; START, Screening Tool to Alert to Right Treatment; SNBHW, Swedish National Board of Health and Welfare; NORGEP, Norwegian General practice; MM, mixed methods; ICU, intensive care unit; MAI, medication appropriateness index.

[a]The study design was not stated but assigned by the authors of this review, considering the methodological procedure described in the study.

[b]Sex proportion and mean age was calculated only for patients exposed to inappropriate medication use.

history of coronary, cerebral or peripheral vascular disease; and vitamin D and calcium supplement in patients with known osteoporosis or previous fragility fracture. Commonly reported PIMs contributing to adverse outcomes related to medications from benzodiazepine, opioid and antipsychotic classes (Appendix 4).

## 3.3 | Association of PIP with outcomes

A total of 39 included studies reported results based on adjusted estimates. The key covariates that were adjusted for included age, sex, disease comorbidities, and number of medications (Appendix 5).

### 3.3.1 | PIPs and mortality

Nineteen studies measured the association between PIP and mortality.[36,37,41,43,48,56,57,60,69,72,77–79,81,82,84–85,93] Four studies reported in-hospital mortality,[48,77–79] the remainder assessed mortality outcome after hospital discharge. Bo *et al*.,[36] apart from reporting the association between the full PIP exposure (inclusive of all types of medications) and mortality, also reported the association of specific PIPs with mortality 6 month after hospital discharge. Full PIP exposure did not have a significant association with mortality; however, the prescription of specific PIPs, such as antipsychotics (adjusted OR [AOR] 1.65, 95% CI 1.12–2.44) and digoxin dosage ≥ 0.125 mg/d (AOR 1.77, 95% CI 1.06–2.98) were associated with higher odds of mortality.

Only 4[36,41,56,69] of 19 studies found an increased risk of mortality from either full or specific PIP exposure. Three meta-analyses for the association of PIPs with mortality were conducted to combine results from different risk estimates. Results from a pooled analysis of ORs did not show a significant difference between PIP users and nonusers (AOR 1.10, 95% CI 0.90–1.36, $P = .35$; Figure 2A), and the same for pooled crude ratios (OR 1.15, 95% CI 1.00–1.31, $P = .05$; Table 2). Similarly, the effect estimates of 2 studies[56,69] evaluating the association of the numbers of PIPs (measured as continuous variable) and mortality, did not produce a significant result (AOR 1.49, 95% CI 0.98–2.26, $P = .06$; Figure 2b), as was for studies reporting risk estimates using hazard ratio (adjusted HR [AHR] 1.02, 95% CI 0.90–1.16, $P = .75$; Figure 2c).

### 3.3.2 | PIPs and hospital readmissions

Eighteen studies provided data on all-cause hospital readmissions.[35–37,39,41,43,45,54,55,57,58,65,68,72,81,82,84,93] Bo *et al*.[36] reported both the associations between full (inclusive of all medications) and specific PIPs exposure with hospital readmissions. Irrespective of the screening criteria and PIP measurement (as dichotomous, continuous and categorical), only 5 of these studies[36,37,41,68,93] demonstrated a positive association between PIPs and hospital readmissions. The number of PIPs (continuous) as predictors of hospital readmission were reported by 5 studies,[35–37,54,55] with only 1 study[37] showing a significant positive association. We did not perform meta-analysis using PIPs as a continuous variable, because summary risk estimates were provided in different formats or studies did not provide sufficient detailed information. Also, PIPs (measured dichotomously) were reported in 13 studies, but only 7 studies[43,45,65,68,81,82,93] gave data suitable for adjusted meta-analysis. The pooled estimate for full PIP exposure and all-cause hospitalisations did not reach statistical significance (AOR 1.11, 95% CI 0.76–1.63, $P = .59$; AHR 1.02, 95% CI 0.89–1.18, $P = .74$; Figure 3) although meta-analysis of the crude odds ratios showed a positive association (OR 1.22, 95% CI 1.03–1.44, $P = .02$; Table 2). The meta-analysis of AOR was associated with a significant heterogeneity ($I^2 = 76\%$) that was minimised on removal of Lau *et al*. ($I^2 = 29\%$, $P = .5$).

### 3.3.3 | PIPs and ADE-related hospital admissions

Overall, 12 studies evaluated the impact of PIPs on medication-related hospital admissions: 7 studies[42,44,47,51,52,74,91] reported the prevalence of hospital admissions due to PIPs (as judged by an expert panel) and 5 studies[38,54,81,86,90] assessed the association between PIPs and ADE-related hospital admissions. A pooled analysis of hospital admissions due to PIP estimated that PIP use was causal or contributory to admission in 11% of patient admissions (95% CI 8–15%). A meta-analysis also showed that PIP use was associated with a 91% increased odds of ADE-related hospital admissions (AOR 1.91, 95% CI 1.21–3.01, $P = .005$; Figure 4a). However, on sensitivity analysis, the association between PIPs and ADE-related hospital admissions was not statistically significant when only the weakest association from a study[90] contributing 4 AOR estimates using various PIP tools, was included in the pooled analysis (AOR 1.65 95% CI 0.75–3.62; $P = .21$).

### 3.3.4 | PIPs and ED visits

Three studies reported the association between PIPs and ED visits, either as a separate outcome[49,57] or as part of a composite outcome.[94] Using an electronic prescribing tool, Forget *et al*.[49] did not show a significant association between the numbers of PIMs and ED visits in the 90 days post hospital discharge, irrespective of frailty status. Likewise, Gutiérrez-Valencia *et al*.[57] reported that the presence of Beers, STOPP or START criteria did not show an association with ED visits at 6 months. By contrast, Wier *et al*.[94] (using a study specific tool) reported that each additional new PIM prescribed at discharge, was associated with an increased risk of composite outcome (ED visit, rehospitalisation, or death) in the 30 days following hospital discharge (AHR 1.13, 95% CI 1.03–1.26). Also, receiving at least 1 new PIM prescription (new PIM users) was marginally associated with the composite outcome (AHR 1.22, 95% CI 1.00–1.49). Alternatively, chronic use of PIMs (e.g. PIMs continued from the community), measured as either discrete or continuous variable, did not show any independent significant association with the composite outcome.

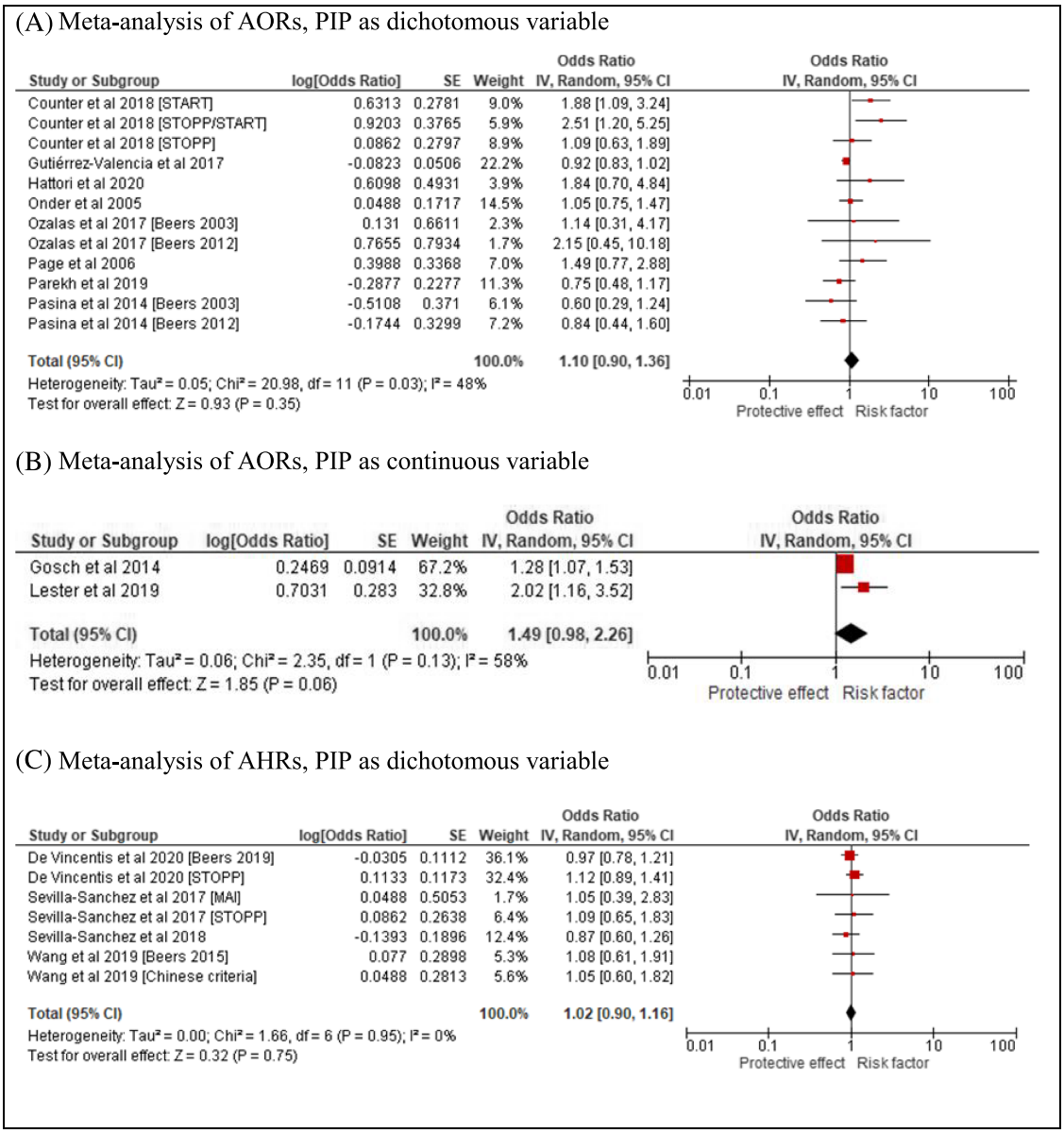


**FIGURE 2** (A) Forest plot of adjusted odds ratio for an association between PIP users (compared with nonusers) and all-cause mortality. (B) Forest plot of adjusted odds ratio for an association between the numbers of PIPs (measured as continuous variable) and all-cause mortality. (C) Forest plot of adjusted hazard ratios for an association between PIP and all-cause mortality. Studies with ≥2 outcome data using various tools are shown with the type of tool. AORs, adjusted odds ratios; AHRs, adjusted hazard ratios; PIP, potentially inappropriate prescribing

### 3.3.5 | PIPs and length of stay

Ten studies described the relationship between PIP and length of stay (hospital or intensive care unit).[49,58,64,69,77–79,84–86] Across the studies, there was no clear association between PIP and length of stay. However, there was some indication that prescription of Beers medications (especially 2 or more) was associated with an increased length of hospital stay.[58,69,77,78] Conversely, 1 study[84] reported that the use of PIM as determined by the STOPP was significantly associated with an increased intensive care unit and hospital stay but no association with the Beers criteria.

### 3.3.6 | PIPs and ADRs/ADEs

Twenty-three studies assessed the impact of PIPs on the occurrence of ADRs/ADEs, either through analysing the association between PIMs and ADRs/ADEs[47,59,67,76–79,81–83,86,89,91,94] or simply reporting only the share of PIMs in the occurrence of ADRs/ADEs.[40,53,63,67,70,71,87,88,95] Links between PPOs and ADRs/ADEs were not reported by any study. Two meta-analyses were conducted to determine the association between PIMs and ADRs/ADEs. The first meta-analysis pooled adjusted odds ratios of the association between PIMs (measured dichotomously) and ADRs/ADEs, indicating that PIM

**TABLE 2** Pooled odds ratio and sub-group analysis, stratified by covariate adjustment, potentially inappropriate prescribing (PIP) tool, country, study design and quality score ($n = 21$)

| | Mortality | | | Hospital readmission | | | ADRs/ADEs | | |
|---|---|---|---|---|---|---|---|---|---|
| **Stratification** [a] | ***n*** | **OR (95% CI)** | **SD ($I^2$), *P*** | ***n*** | **OR (95% CI)** | **SD ($I^2$), *P*** | ***n*** | **OR (95% CI)** | **SD ($I^2$), *P*** |
| **Unadjusted estimates (all studies)** | 19 | 1.15 (1.00, 1.31) | | 15 | 1.22 (1.03, 1.44) | | 7 | 1.80 (1.48, 2.21) | |
| *PIP tool* | | | | | | | | | |
| Beers 1997/2003 | 4 | 1.06 (0.78, 1.43) | 0%, .63 | 1 | 0.77 (0.48, 1.24) | 59.2%, .04 | 2 | 1.77 (1.38, 2.27) | 0%, .61 |
| Beers 2012/2015/2019 | 6 | 1.16 (0.88, 1.52) | | 7 | 1.08 (0.91, 1.30) | | 3 | 1.60 (1.05, 2.44) | |
| STOPP | 4 | 1.04 (0.80, 1.36) | | 4 | 1.75 (1.01, 3.01) | | 1 | 2.78 (1.33, 5.81) | |
| START | 3 | 1.25 (0.82, 1.92) | | 1 | 1.67 (1.18, 2.36) | | 0 | – | |
| Study/country specific | 2 | 1.62(0.95, 2.74) | | 2 | 1.18 (0.87, 1.60) | | 1 | 2.20 (0.84, 5.76) | |
| *Country* | | | | | | | | | |
| America | 4 | 1.90 (1.19, 3.03) | 63.9%, .07 | 0 | – | 22.5%, .26 | 2 | 1.67 (1.14, 2.45) | 0%, .8 |
| Europe | 12 | 1.08 (0.93, 1.25) | | 11 | 1.14 (0.99, 1.31) | | 4 | 1.88 (1.48, 2.40) | |
| Asia | 3 | 1.28 (0.88, 1.85) | | 4 | 1.67 (0.88, 3.19) | | 1 | 1.40 (0.45, 4.36) | |
| *Study design* | | | | | | | | | |
| Prospective cohort | 8 | 1.18 (1.02, 1.36) | 68.5%, .04 | 12 | 1.20 (1.05, 1.37) | 92%, <.00001 | 3 | 2.31(1.46, 3.65) | 0%, .48 |
| Retrospective cohort | 8 | 1.32 (0.98, 1.78) | | 1 | 6.48 (3.00, 14.02) | | 3 | 1.72 (1.37, 2.16) | |
| Cross sectional | 3 | 0.76 (0.53, 1.08) | | 2 | 0.80 (0.58, 1.10) | | 1 | 1.40 (0.45, 4.36) | |
| *Quality score* | | | | | | | | | 0%, .61 |
| 5 | 9 | 1.01 (0.81, 1.25) | 6.2%, .11 | 6 | 1.00 (0.84, 1.19) | 82.3%, .02 | 5 | 1.91(1.42, 2.56) | |
| <5 | 10 | 1.25 (1.07, 1.47) | | 9 | 1.44 (1.13, 1.85) | | 2 | 1.72 (1.30, 2.26) | |
| **Adjusted estimates (all studies)** | 12 | 1.10 (0.90, 1.36) | | 8 | 1.11 (0.76, 1.63) | | 15 | 1.26 (1.11, 1.43) | |
| *PIP tool* | | | | | | | | | |
| Beers 1997/2003 | 4 | 1.03 (0.76, 1.40) | 74.3%, .0004 | 1 | 0.72 (0.43, 1.21) | 25.5%, .26 | 6 | 1.24 (0.98, 1.57) | 22.9%, .27 |
| Beers 2012/2015 | 4 | 0.91 (0.83, 1.01) | | 4 | 0.88 (0.65, 1.18) | | 4 | 1.16 (0.90, 1.49) | |
| STOPP | 1 | 1.09 (0.63, 1.89) | | 2 | 3.16 (0.79, 12.57) | | 2 | 1.65 (0.87, 3.12) | |
| START | 2 | 1.87 (1.16, 3.01) | | 0 | – | | 0 | – | |
| STOPP/START | 1 | 2.51 (1.20, 5.25) | | 0 | – | | 0 | – | |
| Study/country specific | 0 | – | | 1 | 0.99 (0.57, 1.72) | | 3 | 1.38 (1.13, 1.70) | |
| *Country* | | | | | | | | | |
| America | 3 | 1.49 (0.86, 2.58) | 17.5%, .30 | 0 | – | 0%, .54 | 3 | 1.42 (1.06, 1.91) | 4.5%, .19 |
| Europe | 8 | 1.04 (0.83, 1.31) | | 6 | 0.98(0.78, 1.23) | | 9 | 1.14 (0.97, 1.35) | |
| Asia | 1 | 1.84 (0.70, 4.84) | | 2 | 2.00 (0.20, 19.58) | | 0 | – | |
| Others | 0 | – | | 0 | – | | 3 [b] | 1.44 (1.16, 1.78) | |
| *Study design* | | | | | | | | | |

(Continues)

**TABLE 2** (Continued)

| Stratification [a] | Mortality | | | Hospital readmission | | | ADRs/ADEs | | |
|---|---|---|---|---|---|---|---|---|---|
| | *n* | OR (95% CI) | SD ($I^2$), *P* | *n* | OR (95% CI) | SD ($I^2$), *P* | *n* | OR (95% CI) | SD ($I^2$), *P* |
| Prospective cohort | 1 | 0.75 (0.48, 1.17) | 7.7%, .03 | 5 | 1.01 (0.76, 1.35) | 91.3%, <.0001 | 7 | 1.28 (1.07, 1.54) | 42.3%, .18 |
| Retrospective cohort | 9 | 1.29 (0.99, 1.68) | | 1 | 6.56 (2.89, 14.88) | | 5 | 1.37 (1.12, 1.68) | |
| Cross sectional | 2 | 0.72 (0.45, 1.17) | | 2 | 0.75 (0.53, 1.06) | | 3 | 0.93 (0.65, 1.34) | |
| *Quality score* | | | | | | | | | |
| 5 | 6 | 0.90 (0.66, 1.21) | 61.6%, .11 | 4 | 0.84(0.62, 1.14) | 59.4%, .12 | 11 | 1.34 (1.11, 1.63) | 0%, .37 |
| <5 | 6 | 1.17 (0.94, 1.73) | | 4 | 1.65(0.75, 3.63) | | 4 | 1.20 (1.02, 1.40) | |

[a]Data for other outcomes not reported, not enough subgroups;
[b]Canada, Brazil; ADRs/ADEs, adverse drug reactions/adverse drug events; *n*, total number of screenings (>1 screening may be contributed by a single study); SD, sub-group difference; CI, confidence interval; OR, odds ratio.

users (compared with nonusers) were associated with a 26% increase in the odds of ADRs/ADEs (AOR 1.26, 95% CI 1.11–1.43, $P = .0003$; Figure 4a). Likewise, the direction of effect was the same using pooled crude OR (Table 2). The second meta-analysis combined results to estimate the association between PIMs (measured as a continuous variable) and ADRs/ADEs, implying that for every additional PIM, there was a 73% increased odds of ADEs/ADEs (AOR 1.73, 95% CI 1.26–2.37, $P = .0008$; Figure 4b). However, this meta-analysis was associated with significant statistical heterogeneity ($I^2 = 91\%$).

### 3.3.7 | PIPs and functional outcomes

Twelve studies reported the association between PIMs and functional status, expressed in terms of mobility,[34,50,64] hand-grip strength,[62,64] time to functional recovery[48,61] and functional independency.[40,43,46,50,62,64,66,73,89] No study reported these outcomes for PPOs. None of the studies[34,50,64] reported a significant association between PIMs and mobility (measured using the timed up-and-go test). Two studies[48,61] reported that PIM users were significantly associated with longer time to achieve recovery than non-PIM users. The use of PIMs was also associated with lower handgrip strength, which was measured using dynamometer, in 1 study[62] but not in the other study.[64] However, exposure with multiple specific PIMs; that is, a concomitant use of 3 and more psychotropic or opioid medications was associated with reduced hand-grip strength.[64]

Functional independence was measured using various instruments: the Barthel Index[43,50,64,73]; the ADL (activity of daily living) score[40,46,89]; the FIM (functional independence measure) score[66]; and the new mobility score.[62] A meta-analysis of an association between PIMs and functional decline, defined as the loss of independence in at least 1 ADL, was conducted. The pooled estimate showed that the use of PIMs increased the odds of functional decline by 60% (AOR 1.60, 95% CI 1.28–2.01, $P < .0001$: Figure 5). However, this association was not significant on limiting the analysis to include the weakest estimate from studies contributing 2 or more estimates (AOR 1.24 95% CI 0.86, 1.79, $P = .25$).

### 3.3.8 | PIPs and falls

Two studies[73,92] reported falls as an outcome. The prescription of Beers medications was significantly associated the incidence of falls.[92] Similarly, the number of PIMs prescribed (according to STOPP for the Japanese version) was associated with increased occurrence of subsequent falls 1 year after hospital discharge.[73]

### 3.3.9 | PIPs and health-related quality of life

The association between PIPs and health-related quality of life (HRQoL) was reported in 4 studies,[33,34,62,75] all using the EuroQol-5 dimensions (EQ-5D). Two studies[33,75] additionally employed the

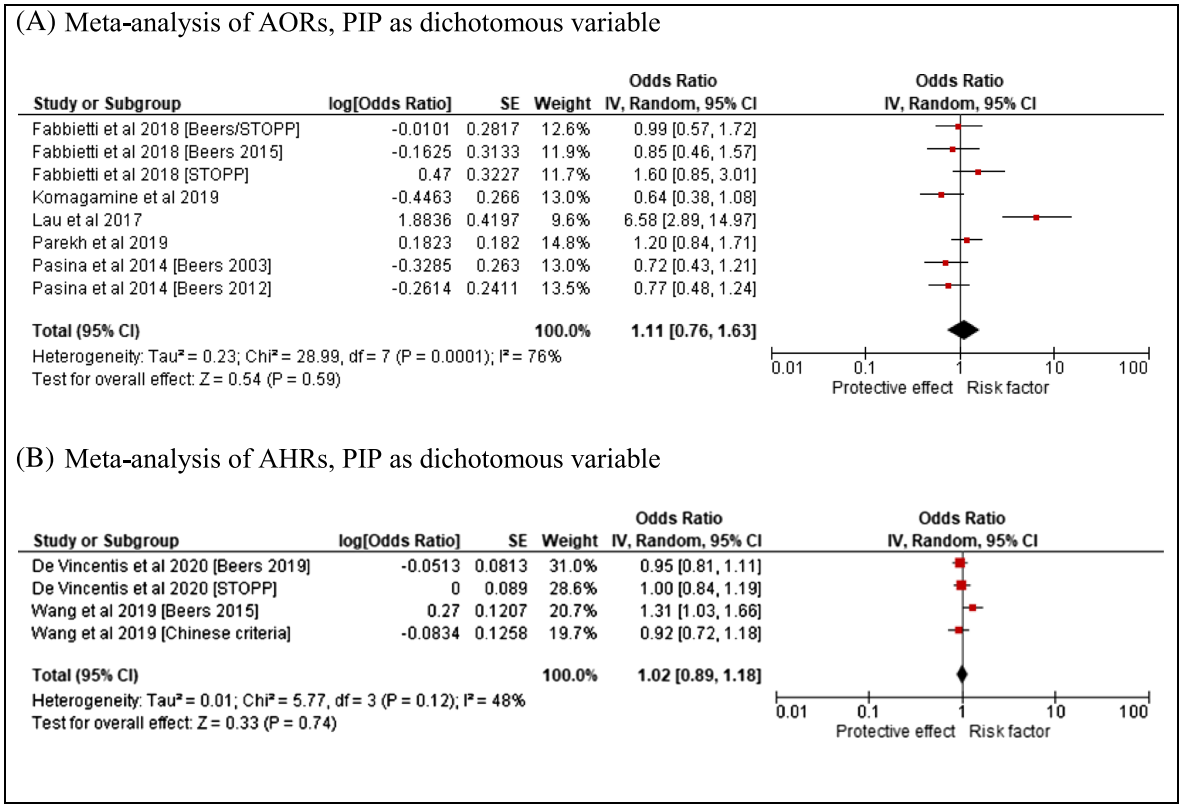


**FIGURE 3** (A) Forest plot of adjusted odds ratios for an association between PIP (measured dichotomously) and all-cause hospital readmission. (B) Forest plot of adjusted hazard ratio for an association between PIP and all-cause hospital readmission. Studies with ≥2 outcome data using various tools are shown with the type of tool. AORs, adjusted odds ratios; AHRs, adjusted hazard ratios; PIP, potentially inappropriate prescribing

EuroQol-Visual Analogue Scale (EQ-VAS) to measure self-rated HRQoL. Using STOPP/START criteria, 1 study[33] did not find a difference between patients who had PIM/PPO and those who did not in associations with EQ-5D index and EQ-VAS. Another study,[75] using the medication appropriateness index (MAI) but the same HRQoL measures, reported lower medication quality was associated with a lower HRQoL. Associations were not clear in the remaining studies; for example, inappropriate medication use (screened via STOPP[34] and a country-specific tool[62]) was significantly associated with reduced HRQoL but only when PIMs were measured dichotomously and only red PIMs (defined as medications that should be avoided irrespective of diagnosis, according to the Danish Criteria[62]) were included, respectively.

### 3.3.10 | Cost implications of PIPs

Three studies reported the economic costs of PIMs.[58,80,88] No studies reported cost implications of PPOs. Hagstrom *et al.*[58] reported those individuals with 3 or more PIMs compared with those with 1 PIM had statistically significant higher hospital costs in the USA. Pardo-Cabello *et al.*[80] evaluated the mean cost of PIMs using STOPP v2 and determined that the cost associated with PIM use was €18.75 ± 4.24 per patient per month (€225.14 ± 50.91 per patient per year), with opioids accounting for the highest percentage of the expenditure. Similarly, Tachi *et al.*[88] calculated the extra cost for treatment of adverse reactions per inpatient who was prescribed drugs listed in the Beers Criteria–Japanese Version and Guidelines for Medical Treatment and its Safety in the Elderly 2015 and was estimated to range from 497 to 13 371 yen per patient (≈7–180 AUD), which corresponds to a national cost of 2.18–381.42 (≈0.03–5 AUD) billion yen per year. Overall, whether the estimation was on total hospital costs, or the extra costs due to PIMs and treatment of PIM-related ADRs, the use of PIM was associated with higher economic cost.

## 4 | DISCUSSION

The systematic review showed a pooled PIM estimate of between 46 and 56%, depending on the tool used, and a pooled PPO estimate of 55% based on the START criteria. Substantial exposure of PIPs during hospital care had significant associations with a range of health-related and system-related outcomes, including medication-related hospitalisation, ADRs/ADEs, functional decline, falls and health care costs. However, based on adjusted estimates, PIP did not show a significant association with all-cause mortality and hospital readmissions. Additionally, inconsistent findings were noted for other outcomes, such as ED visits, length of stay and HRQoL. Most importantly, PIP outcomes were most often related to PIMs; none of the included

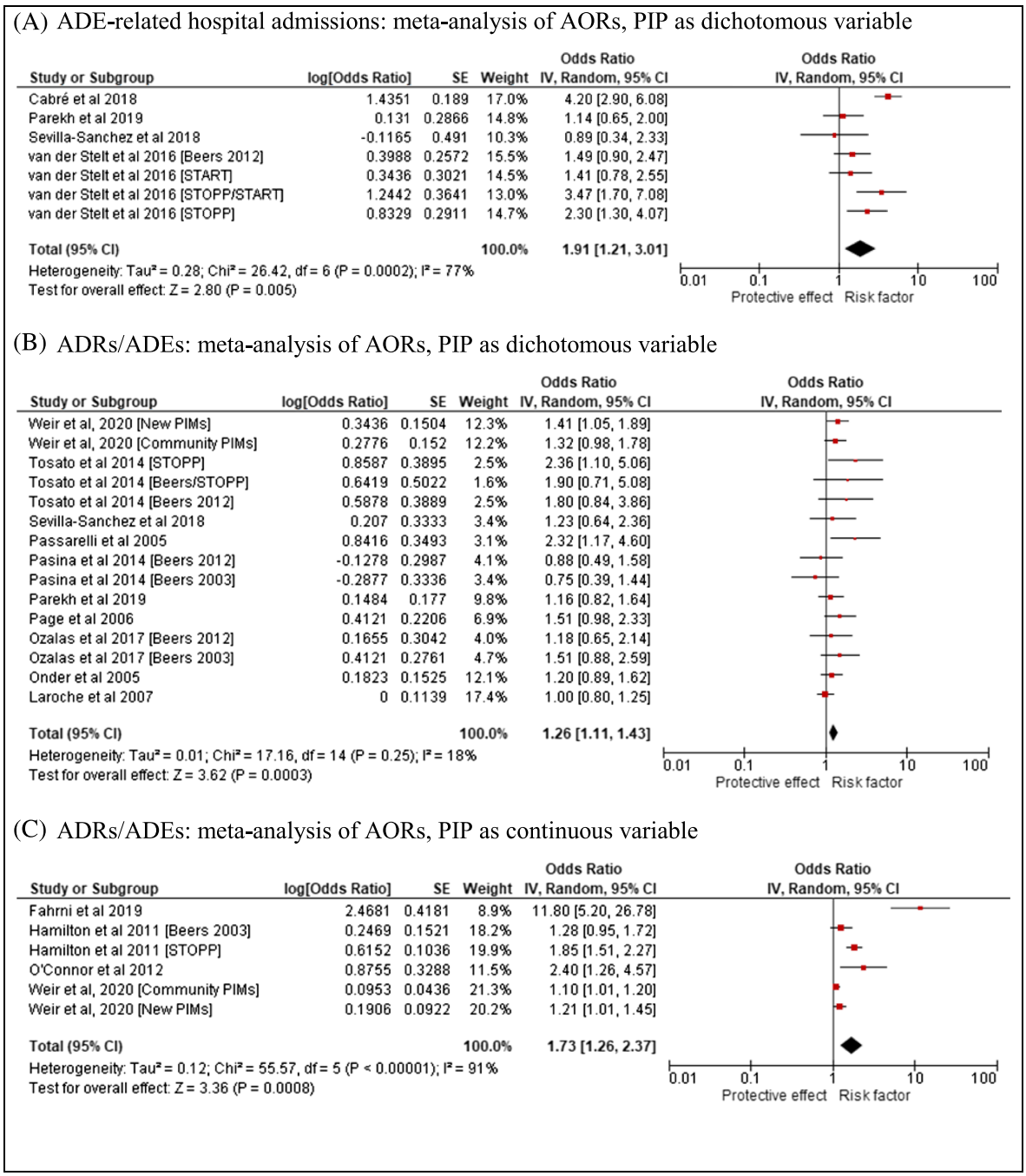


**FIGURE 4** (A) Forest plot of adjusted OR for the association between PIPs (measured dichotomously) and ADE-related hospital admissions. (B) Forest plot of adjusted OR for the association between PIMs and ADRs/ADEs. (C) Forest plot of adjusted odds ratio for the association between PIMs (measured as a continuous variable) and ADRs/ADEs. Studies with ≥2 outcome data using various tools are shown with the type of tool. AORs, adjusted odds ratios; AHRs, adjusted hazard ratios; PIP, potentially inappropriate prescribing

studies explored links between PPOs and ADRs, ADEs, functional decline, falls and cost.

## 4.1 | Comparison with existing literature

Previous systematic reviews have examined associations between PIMs and various outcomes, mainly in heterogeneous healthcare settings, which included community setting, nursing home and hospital,[25–27,96] or only in primary care.[28,97] The findings of our review are consistent with previous reviews on all-cause mortality, but not hospital readmissions. For example, a systematic review and meta-analysis by Xing *et al.*[27] included 33 studies from various healthcare settings reporting that PIMs (identified by Beers and STOPP criteria) were significantly associated with an increased risk of ADRs/ADEs and hospital readmission but not mortality. Likewise,

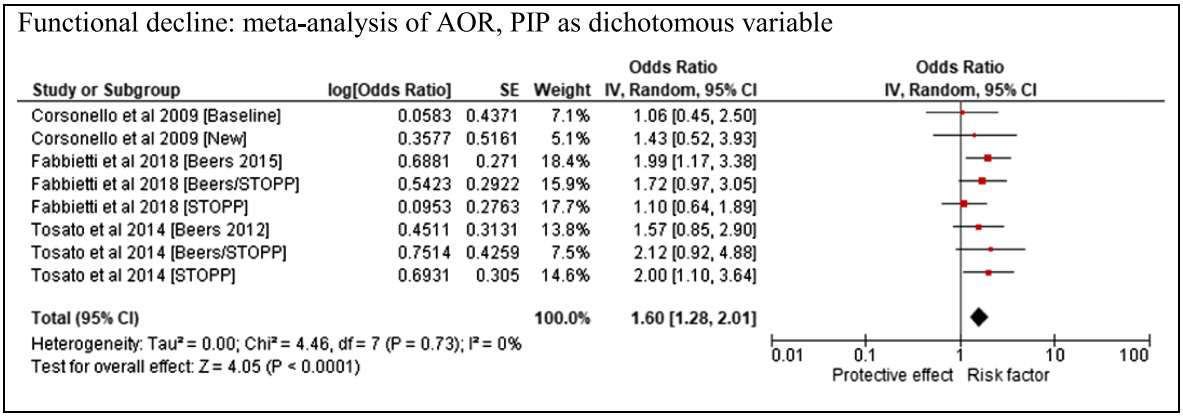


**FIGURE 5** Forest plot of adjusted odds ratio for the association between PIPs (dichotomous) and functional decline. Studies with ≥2 outcome data using various tools are shown with the type of tool. AORs, adjusted odds ratios; PIP, potentially inappropriate prescribing

other reviews have also reported PIPs did not affect mortality[28,96] and yet the impact on hospital readmission was significant, whether in a primary care[28] or across healthcare settings.[26,98]

It should be noted that the methodology used in our review has identified 4 important differences (apart from settings) compared with previous reviews.[25–28,96,97] First, we separately analysed all-cause hospital readmissions from ADE-related admissions. Interestingly, when doing so, there was a significant association between PIPs and ADE-related hospital admissions. The current review found that approximately 1 in 10 hospital admissions were related to PIMs, as a primary or contributory cause. Second, we did not combine risk estimates from various measures of PIP, which typically may lead to erroneous conclusions. Here, we explored the association between PIPs and health-related and system-related outcomes, considering PIPs as a dichotomous variable (PIP users *vs*. nonusers), and the number of PIPs as both a continuous and as a categorical (0, 1, 2 and ≥3 PIP) variable. However, this way of classification was not without challenges, especially when conducting meta-analysis using PIPs as a continuous variable. Very few studies gave data in a suitable format for meta-analysis. Third, meta-analysis was conducted using the full PIP exposure, especially for all-cause mortality, in which 1 study[36] provided data for both full and specific PIPs. While the full PIP exposure did not show a significant association with mortality, the prescription of specific medications, such as antipsychotics and digoxin dosage ≥0.125 mg/d were associated with higher odds of mortality. There is evidence showing that prescriptions of these medications are associated with all-cause mortality.[99,100] Fourth, we pooled data using a random effects model (as opposed to fixed effects) considering the variation in the tools employed to measure PIPs.

Our results found that evidence for the associations between PIP and other system-related outcomes, such as ED visits and length of hospital stay, were inconclusive. This was consistent with findings from a previous review across healthcare settings.[26] However, there is some evidence that PIP in primary care has an association with ED visits.[28] Despite our inconclusive findings about PIP and ED or hospital usage, this review does provide evidence about the association between prescription of multiple PIMs and increased length of hospital stay. In particular, the prescription of PIMs at hospital discharge was significantly associated with composite outcomes (comprising ED visit, hospital readmission and mortality). The higher risk of hospital discharge PIMs (compared to community PIMs) may be due to the possibility of medication discontinuation before patients' hospitalisation if they had already experienced an adverse event.

In the present review, the PIMs that most often contributed to adverse health-related outcomes were medications from benzodiazepine, opioid and antipsychotic classes. These groups of medications have been associated with increased risk of falls.[92,101,102] Although only 2 studies,[73,92] in the current review, assessed the association between full PIM exposure and falls as a primary outcome, detecting a significant positive relationship; many of the included studies[42,44,51,52,74] demonstrated PIMs that increased fall-risk were largely responsible for medication-related hospital admissions. This is particularly important given that >2/3 of medication-related hospital admissions are likely to be preventable.[103]

## 4.2 | Implications for practice and research

The present review suggests that interventions targeting PIM use may prevent medication-related harm and improve health outcomes among hospitalised older adults. Our findings showed significant associations between PIMs and medication-related hospitalisation, ADRs/ADEs and functional decline. Hospitalisation offers an opportunity for medication review and rationalisation although a high rate of PIM, including new PIMs, is also likely at hospital discharge.[44,74] The strength of associations with health outcomes was consistently highest for new PIMs.[94] It is, therefore, recommended to have a comprehensive assessment of medication use, especially during care transitions such as hospital discharge, in order to prevent new PIMs from occurring during the patient's journey, and not cascaded into the community. In contrast, the evidence about associations between PPOs and health outcomes (e.g. ADRs/ADEs, functional outcomes,

falls) are both limited and unclear, hence indicating a need for further studies. Although limited studies evaluated PPOs, the predictive validity of the START criteria for mortality outcome appears promising and needs further investigation.

Deprescribing interventions are generally feasible to reduce PIMs in a hospital setting, but the evidence is limited about the impact on clinical outcomes.[104] In addition to deprescription, strategies to reduce omission of important medications, such as vitamin D and calcium supplementation in patients prone to falls, can reduce risk of fractures and falls.[105] In our current review, the most frequently reported PPOs were vitamin D and calcium supplement in patients with known osteoporosis or previous fragility fracture. It is possible that many PIP-related adverse outcomes are preventable by amalgamating screening tools with practice measures, such as medication reconciliation and medication review.

### 4.3 | Strengths and limitations

This systematic review provides a comprehensive exploration of the association between PIPs and a range of health-related outcomes among older adults in hospital settings. Multiple electronic databases and rigorous screening were used to locate studies evaluating all types of PIP (consisting of PIMs and PPOs), without restricting to specific screening tool for identification of PIPs.

We performed meta-analysis using both adjusted and unadjusted data providing opportunity to examine consistency of the evidence and detect confounding heterogeneity. It is evident that adjusted estimates control confounding, but if used alone may lead to an overestimation of the association.[101,102]

Our review has several limitations that merit consideration. First, there were some studies that did not apply the full screening criteria, mainly those studies employing the Beers criteria. Many of the included studies[40,58,61,79,82,83,87] that employed the different versions of the Beers criteria, only adopted the criteria for PIM use independent of diagnosis. Similarly, there were also studies that did not apply the full version of STOPP.[41,44–46,57,68,80,89,90] These may have caused the heterogeneities and variations in estimates, but we did not perform subgroup analysis based on the completeness of tool because of fewer studies per outcome. Second, included studies varied in terms of adjustment for confounding variables. While many included studies adjusted for multiple confounders, there are still studies that did not sufficiently control for relevant confounders, such as number of medications.[39,45,46,47,54,56,62,68,86,94] The number of medications is the most consistent determinant of PIM use across settings.[106] Also, it is debatable whether the health outcomes are due to the PIPs or the disease/condition itself. Several studies[38,62,68,69,76,79,84,86,87] failed to adjust for comorbidities. The heterogeneity in adjustment may be 1 of the factors why pooled estimates from the adjusted *vs.* unadjusted model vary in the magnitude/direction of effect, specifically for the outcome related to hospital readmissions. Third, combining 2 or more risk estimates from a single study for a same outcome may carry a risk of bias. For instance, sensitivity analyses confirmed that the associations between PIPs and ADE-related hospital admissions, as well as with functional decline were not statistically significant when limiting the analyses to estimates with the weakest association. Fourth, some studies were not designed to investigate the impact of PIPs on health-related outcomes. For example, PIMs were counted as covariates in the assessment of ADRs[38,39,83] or hospital readmission,[41,54] rather than as a primary exposure of interest.

## 5 | CONCLUSION

Our systematic review and meta-analysis revealed a substantial proportion of patients had PIP during hospitalisation and exposure to PIP had a significant association with a range of important health and system-related outcomes in the inpatient hospital setting. These outcomes included medication-related hospitalisation, ADRs/ADEs, functional decline, falls and health care cost. However, PIPs (whether dichotomously or continuously measured) did not show an association with all-cause mortality or hospital readmissions based on adjusted estimates. The impact of PIPs on other outcomes, such as ED visits, length of stay and HRQoL, was inconclusive. PIP-related adverse outcomes are amendable by incorporating common screening tools within interventions designed to optimise older adults' prescriptions at hospital transitions.

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### COMPETING INTERESTS

There are no competing interests to declare.

### CONTRIBUTORS

A.B.M., B.R. and E.M. were involved in conceptualisation, design and framing the research question. A.B.M conducted literature searches, and study selection with B.R. and E.M. helping an independent screening. A.B.M. conducted quality appraisal. A.B.M., B.R. and E.M. were involved in the preparation of the manuscript, including data analysis and interpretation of results. B.C. critically revised the initial manuscript draft for important intellectual content. All authors made suggestions and approved the final version of the manuscript.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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