Are lists of potentially inappropriate medications associated with hospital readmissions? A systematic review

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Running heading: Lists of PIMs and hospital readmissions

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Abstract:

Background

Suboptimal prescribing, including the prescription of potentially inappropriate medications (PIM), is frequent in patients aged 65 years and older. PIMs are associated with adverse drug events, which may lead to hospital admissions and readmissions for the most serious cases. Several tools, known as Lists of PIMs, can detect suboptimal prescription.

Objective

This systematic review aimed to identify which lists of PIMs are associated with hospital readmission of older patients.

Patients and Methods

MEDLINE, Cochrane Library, EMBASE and clinicaltrials.gov were searched for the period from January 1st, 1991 up to May 12th, 2022 to identify original studies assessing the association between PIMs and hospital readmissions or ED revisits within 30 days of discharge in older patients. This study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist and the risk of bias was assessed with the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies (NOS) and the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2).

Results

A total of six studies presenting four different lists of PIMs were included. Readmission rates varied from 4.3 % to 25.5 % and the OR between PIMs and hospital readmission varied from 0.92 [95%CI 0.59; 1.42] to 6.48 [95%CI 3.00; 14.00]. Only two studies found a statistically significant association between a list of PIMs and hospital readmission. These two studies used different tools: STOPP and START and a combination of Beers Criteria® and STOPP and START.

Conclusion

This systematic review shows that the association between list of PIMs and 30-day unplanned readmissions remains unclear and seems dependent on the PIM detection tool. Further studies are needed to clarify this association.

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Key points:

Only two studies found a statistically significant association between PIMs and hospital readmission. These two studies used different tools: STOPP and START and a combination of Beers Criteria® and STOPP and START.

No statistically significant association was found between PIMs and mortality.

The six studies were published between 2017 and 2020, meaning that this is a recent topic, whereas the concept of PIM dates from 1991.

1. Introduction

Due to ageing, patients tend to have multiple comorbidities [1], which in turn require the prescription of several medications and can eventually lead to polypharmacy, which is defined as the use of 5 medications or more [2]. In addition, because of altered pharmacokinetics and pharmacodynamics, older patients may suffer from suboptimal prescribing [3], which is classified in 3 main types of risk: excessive treatment ("overuse"), insufficient treatment ("underuse") and potentially inappropriate medications ("misuse") [3]. Potentially inappropriate medications (PIMs) are medications for which associated risks outweigh potential benefits when they are prescribed in a population of older patients [4].

Many strategies and tools have been proposed to detect PIMs in older people's prescriptions. These tools can be categorized in two main types: explicit and implicit tools. Explicit tools are lists of drugs. The first was developed by Beers *et al*. in 1991 in the United States [5] with a Delphi method involving 13 nationally recognized experts. This list was updated in 2012 [6], 2015 [7] and 2019 [8]. This tool was also adapted in many countries to fit the prescription habits and available drugs of each country, such as the Laroche list in France [9] or the Priscus list in Germany [10]. The other type of tools is the implicit tools, which are recommendations for practice, based on clinical reasoning, consideration of comorbidities and drug-drug interactions. The most used implicit tools are STOPP and START [11] developed in 2008, and updated in 2015 [12] and the Medication Appropriateness Index (MAI) [13], developed in 1992. Both explicit and implicit tools are useful for physicians and pharmacists as they make it possible to rapidly identify PIMs and thus consider their discontinuation [14].

PIMs are associated with adverse drug events, which may lead to hospital admissions and readmissions for the most serious ones [12,15,16]. Despite the fact that this risk is well-known, almost 50 % of elderly patients have at least one PIM on their prescription [17].

Elderly patients are frequently readmitted: about 14 % of them have an unscheduled admission within 30 days after the discharge of a first admission [18]. These readmissions are harmful for the patients, as they increase the risk of morbidity, mortality and dependency but are also a heavy burden for the healthcare system through overloaded emergency departments and increased healthcare expenditure [19,20].

In their systematic review, Hansen *et al*. [21] have shown that clinical interventions conducted during patient care can reduce readmissions, however, none of the clinical interventions described in their systematic review has considered PIMs.

Therefore, the main objective of this systematic review was to define which lists of PIM are associated with hospital readmissions. The secondary objectives were to describe the readmissions of patients with PIMs (delay before readmissions, type of readmissions, and length of stay of the index admission) and to define which lists of PIMs are associated with risk of death.

2. Method

This study is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist [1].

The protocol was registered in the Prospero database [CRD42021252107]. There was no modification to the protocol.

2.1. Eligibility criteria

We have included all original interventional and observational comparative studies assessing the association between PIMs and hospital readmissions or ED revisits within 30 days after discharge in older patients defined as patients aged 65 or over. All tools (explicit or implicit) were eligible. Studies on older patients with specific pathologies or conditions (e.g. surgical, specific psychiatric diseases) were excluded. Case studies, systematic reviews, non-research articles and abstracts from conferences were excluded.

2.2. Search strategy

We searched the following electronic databases for the period from January 1st, 1991 to May 12th, 2022: MEDLINE via Pubmed, Cochrane Library, EMBASE and Clinicaltrials.gov. The year 1991 corresponds to the first publication of the Beers criteria®, which is the first published PIM list [1]. Key search terms related to aged patients were combined with terms related to PIMs and with those related to hospital readmission. We did not use language restriction. The search equation is reported in Supplementary data 4.

2.3. Selection process

After duplicate removal, titles and abstracts were screened by two independent reviewers (AC & CS). Studies identified for full-text review were assessed independently by these two reviewers (AC & CS) with the help of a third reviewer (PH) to resolve disagreements. To decide whether a study met the defined inclusion criteria, an evaluation grid was developed with the selected items: original article, comparison between 2 groups, study population aged 65 or over, no specific pathologies or conditions, PIMs identified by a list, reporting of 30-day hospital readmissions or ED revisits.

2.4. Data collection process

Data collection was performed by one reviewer (AC) using a predefined data extraction form. If insufficient details were reported, study authors were contacted for further information.

2.5. Data items

For each included study, the following variables were collected:

- General characteristics: journal, year of publication, funding source
- Setting: country, number of centers
- Study design (prospective or retrospective, cohort or randomized controlled trial and multicentric or monocenter)
- Population characteristics: inclusion and exclusion criteria, sample size, mean age, male/female ratio, number of participants in each group, length of stay of the index admission
- The tool used for assessing the list of PIMs

- Data collection process for the outcome (*e.g* telephone interview with the patient or data from the electronic medical record)
- Outcomes: 30-day hospital readmission or ED revisit rate, 30-day mortality rate, in both groups and the crude, and adjusted when available, odds ratio (OR) for the association between PIMS and hospital readmission . We also collected the description of the readmissions (delay before readmission, type of readmission (ED revisits or hospitalizations)
- Presence of confounding factors accounted for in adjusted analyses (*e.g* polymedication, comorbidities, age).

We tried to contact the authors to collect information in the case of unclear or missing data in the article.

2.6. Risk of bias assessment

One reviewer (CS) assessed the risk of bias of each study using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies (NOS)[22] and the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)[23].

The level of evidence was evaluated using the GRADE approach [24].

2.7. Synthesis methods

We described the characteristics of included studies.

We reported crude OR for hospital readmissions rates when available, with an OR>1 suggesting a higher risk of re-admission with a higher number of PIMs. The crude OR could also be calculated from the number of readmitted patients and the number of patients exposed to PIMs.

The crude OR were presented graphically in a forest plot. The forest plot was stratified according to the tool used for assessing list of PIMS.

R (version 4.2.0) was used to synthesize results (library meta, metabin).

3. Results

3.1. Study selection

We identified 1,579 references from the four databases. After removal of 449 duplicates, we screened 1,130 studies based on titles and abstracts, leading to the exclusion of 1,088 irrelevant publications. A total of 42 full-texts were independently reviewed for eligibility and six studies, meeting the eligibility criteria, were included (Figure 1).

3.2. Study characteristics

The characteristics of selected studies are presented in Table 1. The six studies were published between 2017 and 2020. Three were conducted in Asia [25–27] (Japan and China), two in North-America [28,29] (United-States and Canada) and one in Europe [30] (Italy). Among the six studies, three were prospective observational cohort

studies [25,29,30], two were retrospective observational cohort studies [27,28] and one was a randomized controlled trial [26]. Half of the studies were monocentric [25–27].

Patients were 65 years old or over, except in one study where they were 75 years old or over [27]. Mean age varied from 76 to 83.5 years old (Table 1). The sample size varied from 165 to 25,190 patients.

The setting differed between studies. Two studies were conducted in university-hospitals [28,29] and four were conducted in general hospitals [25–27,30]. In the studies conducted in general hospitals, the patients were hospitalized in medical wards [25–27,30] whereas the patients were either hospitalized in medical or surgical wards or even in an intensive care unit, during the index admission for the studies conducted in university-hospitals [28,29]. The medical wards were units of internal medicine [25,30], geriatric unit [26] or all the medical wards of the hospital [27]. The duration of the studies varied from 30 days to 6 years.

3.3. Risk of bias

As depicted in table 2, the observational studies [25,27–30] were of an overall good quality despite confounding bias, except Basnet *et al.* which was of an overall poor quality. This overall poor quality is mainly explained by the assessment of the outcome since it was collected from the electronic medical records, the readmissions occurring in another hospital could indeed be missing from electronic medical records. Furthermore, there was no statement about the follow-up of the population in this study.

The randomized study [26] has also an overall high risk of bias: the randomization process, deviations from the intended interventions and missing outcome data were rated at high risk of bias (Figure 2).

Based on the GRADE approach, we found that the level of evidence for this research question was very low for the following reasons: lack of randomized controlled trials, inconsistency across populations, study design, criteria used and definition reported, with a high level of heterogeneity.

3.4. PIM lists

As shown in table 1, the tools used to identify PIMs differed between studies. Two studies used the explicit Beers Criteria® [25,28] and two studies used an implicit tool (MAI and STOPP and START) [26,27]. Besides, one study used both an implicit and an explicit tool, separately (Beers criteria® and STOPP and START)[30]. Finally, one used a combination of Beers criteria® and STOPP and START [29].

Concerning the explicit criteria, four studies used the Beers Criteria® [25,28–30] from different versions: Basnet *et al.* [28], published in 2018, used the version of 2012, Komagamine *et al.* and Weir *et al.* , published in 2019 and 2020 respectively, used the 2015 release and De Vincentis *et al.* [30], published in 2020, used the 2019 version. The implicit tools used were the MAI and STOPP and START. The MAI was used in one study [26] and STOPP and START was used in three studies [27,29,30]. These three studies used the second version of STOPP and START.

The percentage of patients with PIMs varied between studies. Weir *et al.* had the highest percentage, 65.6 % of patients with PIMs with a combination of Beers and STOPP criteria [29]. The two lowest percentages of patients with PIMs were 25.7 % and 27.3 %, both using STOPP and START[27,30].

3.5. Outcomes

In three of the six studies, the primary objective was to evaluate the association between PIMs and readmission rates. In the remaining three studies, it was a secondary objective (Table 1). The definition of readmission differed between studies: for three of the six studies, all hospital readmissions were considered [25,28,30]. For Chiu *et al.* [26] only unplanned readmissions were considered and for Lau *et al*. [27], emergency readmissions only were considered. Weir *et al.* [29] considered both hospital readmissions and emergency department revisits (Table 1).

The outcome was mainly collected from the electronic medical records of the patients. One study used a healthcare administrative database and another one used a phone interview (Table 1).

Readmission rates varied from 4.3 % to 25.5 %. In the six studies, the OR between PIMs and hospital readmission varied from 0.92 [95%CI 0.59; 1.42] [30] to 6.48 [95%CI 3.00; 14.00] [27]. Only two studies found a statistically significant association between PIMs and hospital readmission [27,29]. These two studies used different tools: STOPP and START and a combination of Beers Criteria® and STOPP and START (Figure 3).

Among the five observational studies, only three adjusted on potential confounding factors. In Komagamine *et al.*[25], the cofactors accounted for were gender and the Charlson comorbidity index. In Lau et *al.* [27], the cofactors were gastrointestinal disorders and gout. The adjustments did not significantly modify the results: in Komagamine *et al.*, the OR changed from 0.93 [95%CI 0.46 – 1.87] to 0.78 [95%CI 0.36 – 1.66] and from 6.48 [95%CI 3.00; 14.00] to 6.557 [95%CI 2.889 – 14.971] in Lau *et al*. (Supplementary data 1).

One of our secondary objectives was to describe readmissions (time before readmission, type of readmission, length of stay). Unfortunately, none of the studies selected for the review described readmissions. Only the Komagamine *et al.* [25] and the De Vincentis *et al.* [30] studies reported median lengths of stay : 13 [Q1-Q3 :7-25] and 9 [IQR = 8] days, respectively (Supplementary data 3).

Finally, only three studies [26,29,30] assessed an association between PIMs and mortality, which was not statistically significant in any of these three studies (Supplementary data 2).

4. Discussion

Our systematic review of the literature retrieved six studies evaluating the association between PIMs and 30-day readmissions among elderly patients. Only two studies showed a significant association: Lau *et al*. [27] using the implicit tool STOPP and START and Weir *et al.* [29] using a combination of the explicit Beers criteria® and the implicit tool STOPP and START.

The six studies were published between 2017 and 2020, meaning that this is a recent topic, whereas the concept of PIM dates from 1991. Interestingly, public health policies have also recently focused on the burden of hospital readmissions (e.g. the Readmission Reduction Program in the United States dates from 2012 [31]). As risk factors for unplanned readmissions remained unknown and risk scores lack sensitivity [32], the participation of PIMs in the risk of readmission was interesting to explore. The six studies were published in diverse continents of the world: Asia, North America and Europe.

The population in the six studies had a mean age varying from 76 to 83.5 years old, the majority of them were women, which is consistent with the worldwide geriatric population. Readmission rates varied between studies, from 4.3 % [30] to 25.5 % [27] which is consistent with that found in the literature [33]. The variation across studies may be explained by the definition of the outcome. Some studies indeed only considered unplanned readmissions [25] whereas others considered both ED visit and readmissions [29]. The data collection method can also influence the outcome, as the readmissions occurring in another hospital could be missing from electronic medical records [34].

The proportion of patients with PIMs among the total number of patients also varied between studies: from 25.7 % [30] to 65.6 % [29]. Lau *et al.* [27] and De Vincentis *et al.* [30] found the lowest percentage of patients with PIMs; 25.5 % and 25.7 %, respectively. They both used the implicit tool STOPP and START. This implicit tool is based on clinical reasoning and takes into consideration comorbidities and drug-drug interactions. Comorbidities or other prescribed drugs might not all be recorded in the electronic medical records, leading to an underestimation of the number of PIMs. The study with the highest percentage of patients with PIMs (65.6 % of patients with PIMs) used a combination of the explicit Beers criteria® and the implicit tool STOPP and START [29], resulting in the addition of different criteria. The studies only using the explicit Beers criteria® found a percentage of patients with PIMs varying between 31.1 % [30] and 55.0 % [28]. The implicit tool MAI was used in only one study (41.8 % of patients with PIMs), certainly because this tool is difficult to implement in daily practice, as it consists of a list of ten questions for each prescribed drug [13].

The mean percentage of patients with PIMs remains high in elderly patients despite the fact that PIMs are known to generate higher costs of hospitalization, health care expenses, and visits to an emergency department owing to adverse drug reactions [35]. Clinical interventions, such as medication review or educational interventions have already proven their effectiveness to reduce the PIMs rate in older patients [36]. Future public health policies are needed to implement the appropriate use of medications in the elderly.

In this systematic review, only two studies among six have found a significant association between PIMs and 30-day readmissions. Weir *et al*. [29] used a combination of the implicit tool STOPP and START and the explicit Beers criteria® leading to a high rate of patients with PIMs (65.6 %) whereas Lau *et al.* [27] have only used the implicit STOPP and START tool, leading to a lower rate of patients with PIMs (27.3 %).

De Vincentis *et al.* [30] have also used the STOPP and START implicit tool but found no significant association between PIMs and readmission, This might be related to the very low readmission rate in this study (4.3 %) as some readmissions were not taken into account, such as the ED revisits. In the Chiu *et al*. study, the association between PIMs and readmissions was a secondary objective and the tool used to detect PIMs was MAI. The number of included patients may not have been sufficient or the tool not designed to detect the association. Moreover, implicit tools are based on clinical reasoning. Each clinician can thus make his own interpretation of the tools. Patients identified with PIMs could be very different between studies, which may explain why they are associated with greater differences in readmission. Finally, the three studies using the Beers criteria did not find any association between PIMs and readmission. Studies should be conducted in order to further explore this finding.

Among the six included studies, three have also assessed the association between PIMs and mortality within 30 days of discharge. These studies report similar results with no statistically significant association between mortality and PIMs, which is consistent with the systematic review from Xing *et al.* [37].

4.1. Limitations

Our systematic review has some limitations. First, the included studies had heterogeneous practice, settings and populations. The type of readmission also differed between studies, which may have influenced the readmission rates. Because of such differences across studies, a meta-analysis was not feasible. Further studies assessing an association between PIMs, detected with STOPP and START in particular, and 30-day unplanned readmissions should be conducted to compare with the studies from Lau *et al.* [27] and De Vincentis *et al.* [30] in order to unravel the discordant results between these two studies.

The use of PIMs tools may have varied across included studies: tools used on the discharge prescription only *vs* through the entire stay, length of PIMs prescription considered "positive" (one PIM occurrence only in the entire stay *vs* multiple days PIMs prescriptions). These variations may have influenced the results obtained by authors.

Finally, we only included studies assessing the association between PIMs and 30-day readmissions. We could have extended the time to readmission over 30 days in order to retrieve more studies. However, readmissions occurring after 30 days post discharge may reflect the exacerbation of complications of chronic diseases more than a poor organization of the patients' care pathway and thus the interest of PIMs, as depicted by the World Health Organization [38].

5. Conclusion

Assessing the association between PIMs and readmission of aged patients seems quite new: the articles reported in this review were published between 2017 and 2020. This systematic review shows that the association between PIMs and 30-day unplanned readmissions remains unclear and seems dependent on the PIM tool. Further studies are needed to clarify this association. It would indeed be interesting to investigate the association between the number of PIMs per patient, as well as their pharmaceutical class, and the risk of readmission. Some pharmaceutical classes are indeed more related to specific adverse drug events, nervous system drugs are, for example, known to cause falls.

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Author contributions

Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data: Camille Schwab, Alice Clementz, Patrick Hindlet, Agnès Dechartres

Drafting the article or revising it critically for important intellectual content: Camille Schwab, Alice Clementz, Patrick Hindlet, Christine Fernandez

Final approval of the version to be published: Agnès Dechartres, Christine Fernandez, Patrick Hindlet

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Figures

Figure 1: flow diagram of the selection process

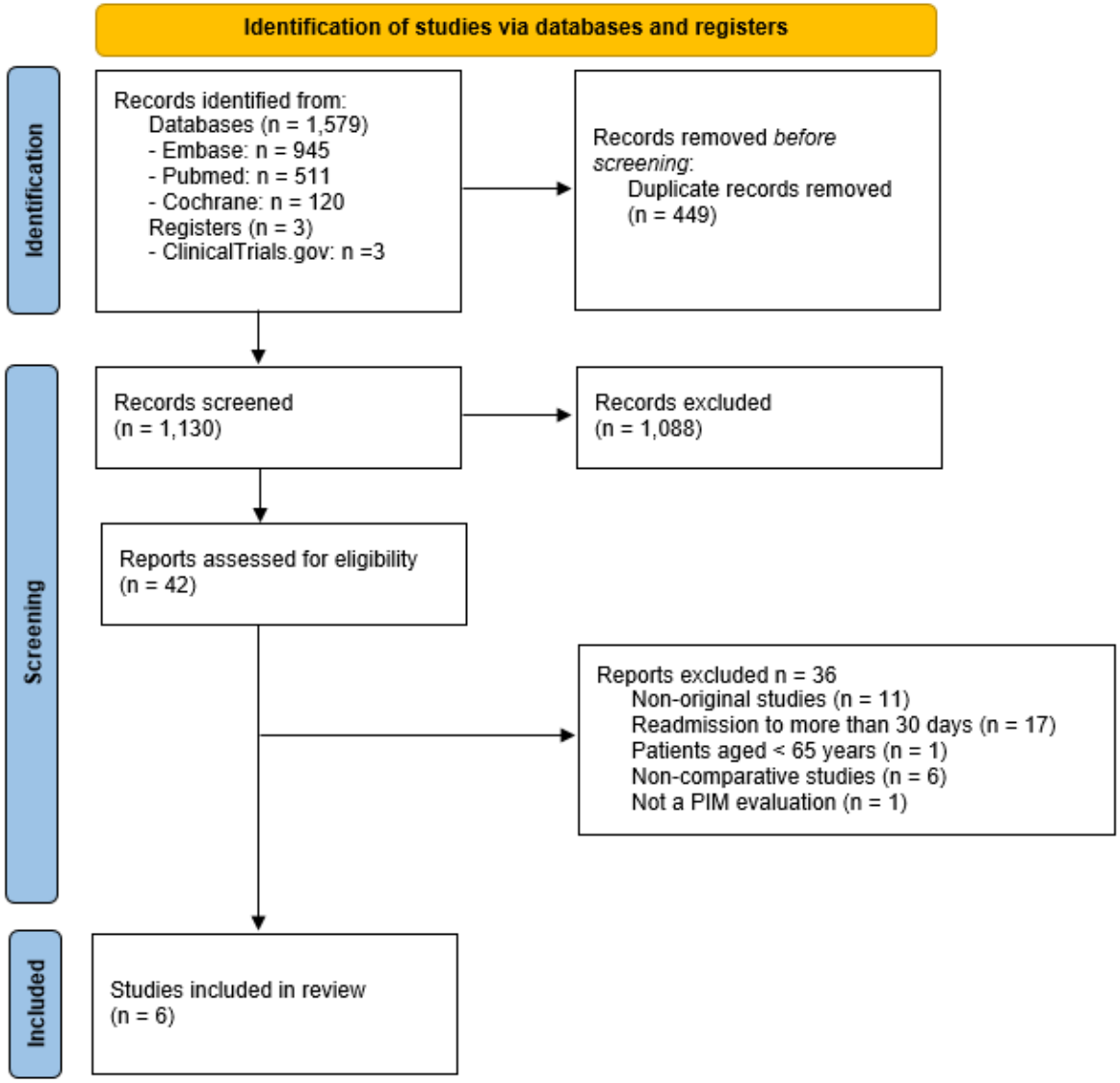


Figure 2: Risk of bias of randomized studies according to Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

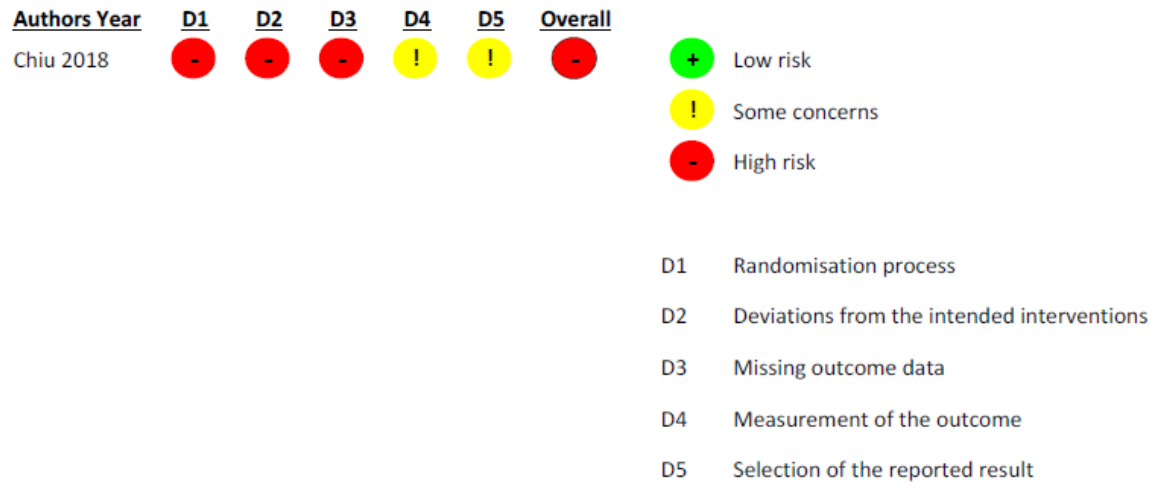
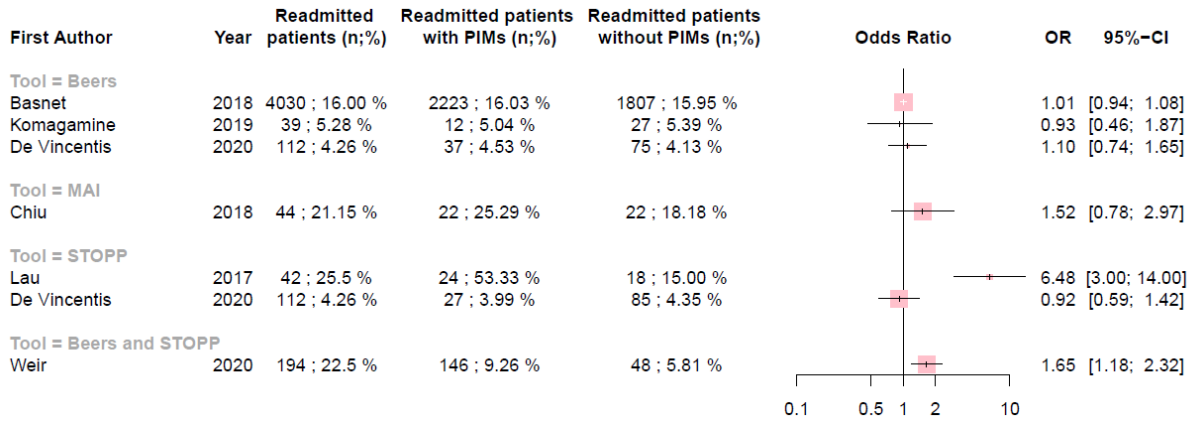


Figure 3: Forest plot of Odds Ratio for readmission risk between patients with and without PIMs according to the tool used



OR = Odds Ratio, CI = Confidence Interval

STOPP = STOPP and START tool

Tables

Table 1: Characteristics of the included studies

First author Year Country	Design	PIM list	Setting	Association between PIMs and 30-day readmissions	Type of readmissions	Data collection method	Population		
							Sample size (number of patients)	Mean age (yo)	% of women
Basnet 2018 USA	Retrospective cohort, multicentric (n=2 hospitals)	Beers (2012)	Medical, surgical wards or ICU	Secondary objective	Hospital readmissions	Electronic medical records	25,190	NA	55.0
Komagamine 2019 Japan	Prospective cohort, monocentric	Beers (2015)	Internal medicine wards	Primary objective	Hospital readmissions	Electronic medical records	739	82.0	52.6
Chiu 2018 China	Prospective RCT, monocentric	MAI	Geriatric wards	Secondary objective	Unplanned hospitalisation	NA	208	83.3	51.9
Lau 2017 China	Retrospective cohort, monocentric	STOPP (v2)	Medical wards	Primary objective	Emergency readmission	Electronic patients records	165	83.5	60.6
Weir 2020 Canada	Prospective cohort, multicentric (n=2 hospitals)	Beers (2015) and STOPP (v2, 2015)*	Medical or surgicals wards	Primary objective	ED visit or rehospitalisation	Healthcare administrative database	2,402	76.0	42.5
De Vincentis 2020 Italy	Prospective cohort, multicentric (n=107 wards)	Beers (2019) or STOPP (v2, 2015)	Internal medicine wards	Secondary objective	Hospitalisation	Phone interview	2,631	79.0	51.4

[a]USA = United States of America, [b]RCT = Randomized controlled trial, [c]PIM = potentially inappropriate medication, [d]MAI = Medication Appropriateness Index, [e]STOPP = STOPP and START, [f]combination of Beers and STOPP and START, [g]ICU = intensive care unit, [h]ED = Emergency Department, [i]NA = Not Available, [j]Simple size: number of patients, [k]yo = years old,

Table 2: Risk of bias of observational studies according to Newcastle-Ottawa Quality Assessment Scale for Cohort Studies

Authors **Year**	**Basnet** **2018**	**Komagamine** **2019**	**Lau** **2017**	**Weir** **2020**	**De Vincentis** **2020**
Design	Cohort	Cohort	Cohort	Cohort	Cohort
Selection	★★★	★★★	★★★	★★★★	★★★
Comparability			★	★	★★
Outcome/Exposure	★	★★	★★★	★★★	★★★
Overall risk of bias	Poor quality	Good quality	Good quality	Good quality	Good quality

High quality choices are identified with a star for each item.