Which Potentially Inappropriate Medications list can detect patients at risk of readmissions in the older adult population admitted for Falls? An observational multicentre study using a clinical data warehouse Running heading: Potentially Inappropriate Medications and Readmissions • Authors

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ABSTRACT

Objective Hospital readmissions are common in the older adult population and potentially inappropriate medications are known to be involved in these readmissions. Several lists of potentially inappropriate medications have been published in diverse countries in order to adapt the lists to local specificities. Among them, the Beers Criteria® were first published in 1991 in the USA, followed by the French Laroche list, the Norwegian NORGEP criteria, the German PRISCUS list, the the Austrian consensus panel listand the European list, EU-7. The main objective was to detect which potentially inappropriate medications list can better detect hospital readmissions within 30 days in the older adult population hospitalized for fall related injuries.

Methods A multicenter observational retrospective cohort study was conducted. Data from older patients initially hospitalized for falls in 2019 and discharged home, were retrieved from the clinical data warehouse. Exposure to potentially inappropriate medications was classified according to the six lists mentioned above.

Results After adjustments using propensity score matching, taking a potentially inappropriate medication as per Laroche and PRISCUS lists was associated with a 30-day hospital readmission with an OR of 1.58 (95 % CI [1.06-2.37]) and 1.68 (95 % CI [1.13-2.50]) respectively while the other 4 studied lists showed no association with readmissions.

Conclusion Our study evidenced that not all lists published allow the accurate prediction of hospital readmissions to the same extent. We found that Laroche and PRISCUS lists were associated with increased 30-day all-cause hospital readmissions after an index admission with a FRI.

The local ethic committee approved the study protocol (number CER-2020-79).

STATEMENTS AND DECLARATIONS

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KEY POINTS

Not all published Potentially Inappropriate Medication lists accurately predict hospital readmissions. Potentially inappropriate medications using the French Laroche and the PRISCUS lists were associated with increased hospital readmissions after an index admission for fall.

1) INTRODUCTION

Worldwide, the proportion of the older adult population is increasing. It reached around 20% and 16% of the American and French population respectively in 2018 [1]. By 2050, the proportion of the older adult world population is expected to increase from 8 % to 16 %. One of the main health concerns of the older age group is fall related injuries (FRI) [2]. According to a World Health Organization (WHO) report on falls, 28-35% of people aged 65 and older fall each year; this percentage increases to 32 % - 42 % for people aged 70 years and older [3]. Therefore, the likelihood of falling increases with age [2]. Falls may have multiple causes; certain medications are called falls-related drugs due to their induced risk of orthostatic hypotension in antihypertensive drugs, sedation and dizziness in psychoactive drugs for instance [4].

The majority of the older adult population suffer from comorbidities which are defined as the presence of multiple chronic diseases [5]. Consequently, several medications are required, thus putting the older adult population at risk of polypharmacy, defined, by most definitions, as 5 medications or more [6]. Because of alterations in pharmacokinetics and pharmacodynamics, some drugs have a low benefit-to-harm risk ratio when prescribed for older patients. These medications are called potentially inappropriate medications (PIM). PIMs increase the risk of adverse drug events (ADE) which occur more frequently in the older population [6,7]. These ADEs can lead to hospital admissions and readmissions [8]. Several lists of PIMs have been published in diverse countries or regions in order to adapt the lists of PIMs to local specificities. Among them, the Beers Criteria® were first published in 1991 in the USA, followed by the French Laroche list, the Norwegian NORGEP criteria, the German PRISCUS list, the Austrian consensus panel listand the European list, EU-7 [9–14].

Hospital readmissions are common as up to 21.5 % of older patients were readmitted. A hospital readmission is defined as a new admission within a specified time frame after discharge, following an index admission. The hospital readmissions within 30 days are considered as an indicator of the quality of care and the performance of the hospital. A history of fall is an important risk factor for hospital readmission: a study, based on the WHO database and the National Readmission Database (NRD) in the United States, showed that older patients with a tendency to fall were 4.5 times more likely to be readmitted to the hospital compared to the patients who did not tend to fall [15]. Another large cohort study, representing 8.3 million Medicaire beneficiaries, was conducted to

compare FRIs to other readmission diagnoses. In this study, Hoffman *et al*. showed that 12.9% of patients with records of previous falls were readmitted to the hospital, ranking FRIs as the third leading readmission diagnosis representing 5.1% of all readmissions [16].

In a systematic review, Morabet *et al.* have shown that 3 to 64 % of readmissions are drug-related, and PIMs are known to be involved in these readmissions [17,18]. However, as PIM lists are diverse, we wondered whether they could be considered equivalent for the identification of patients at risk of readmission.

The aim of our study was to detect which PIM list is more efficient at detecting patients at risk of hospital readmissions within 30 days in the older population hospitalized for FRI. Secondary objectives were the identification of the most prevalent PIMs according to each list, the assessment of a correlation between the number of PIMs and the time to readmission and to assess the list which is the most efficient at detecting patients at risk of hospital readmissions within 7 days.

2) METHODS

This study is presented according to the REporting of studies Conducted using Observational Routinely-collected health Data for Pharmaco-Epidemiology (RECORD-PE) statement [19] (Table S7).

2.1) Study Design and Data Source

A multicenter observational retrospective cohort study representing older patients initially admitted with a diagnosis of FRI was conducted from January 1st to December 31st 2019, using the Clinical Data Warehouse (CDW). In addition to demographic data, the warehouse comprises medico-administrative data from the PMSI (medicalized information system program), diagnoses, procedures, biology and imaging results and medical reports associated with hospital admissions, including emergency department data.

2.2) Study Participants

The included patients were aged 75 years or over admitted to one of the 11 hospitals with a diagnosis of FRI according to the International Classification of Diseases, 10th Revision (ICD-10) and discharged home (Figure 1). The ICD-codes for FRIs are presented in the supplementary materials (Table S1).

The exclusion criteria were patients who died during the hospital stay or within 30 days of discharge. Deaths after discharge were verified in the national open dataset of death records [20].

2.3) Data handling and method of measurement

Included patients were divided into two groups: exposed and non-exposed to PIM. Medications were classified as PIMs according to each of the following seven lists: the American Beers Criteria®, the French Laroche list, the Norwegian NORGEP criteria, the German PRISCUS list, the Austrian consensus panel list and the European list, EU-7. These lists are mainly explicit which means they are criteria based as compared to implicit lists which need a clinical judgment. In our study, only explicit criteria are taken into consideration because of their ease of use and implementation compared to the implicit criteria lists. We chose to compare these lists because the Beers Criteria® is widely used, the French Laroche list is applicable for the French population and the other 4 lists are all appropriate for each European country. The PRISCUS, Austrian consensus panel and EU-7 lists included only single drugs without any combinations as compared to the remaining 3 lists studied.

Beers Criteria® was first developed in 1991 to determine inappropriate medication in patients residing in nursing homes in the United States. It was later updated to be applicable to all patients aged 65 years and older. Currently, the American Geriatric Society (AGS) Beers Criteria® is a widely used tool that includes a list of PIM use in older adults (65+). This tool has been updated 5 times to date. The latest update was in 2019. All of Beers Criteria® was assessed for our study population except for the following: “Drugs to be used with caution in older adults” [9].

The French Laroche list was created in 2007 to make the PIM lists available at that time more easily applicable to the French population. The list is appropriate for people aged 75 years and older. All 34 criteria, including single medications and drug-drug and drug-disease interactions, were assessed in the French Laroche list [10].

The NORGEP criteria was created in 2009 for the Norwegian population aged 70 and above. All 36 criteria were assessed in our study population [11].

The PRISCUS and Austrian consensus panel lists were created in 2010 and 2012 respectively. Both lists apply to people aged 65 years and above and to their respective countries. All 83 drugs in the PRISCUS list and 73 drugs in the Austrian panel consensus list were studied [12,13].

The purpose of the European Union study was to develop one list that covers the drug market of seven European countries (Germany, Finland, Estonia, the Netherlands, France, Spain and Sweden). It was created in 2015, including 282 chemical substances (34 therapeutic groups). All criteria were analyzed in our study population [14].

We have studied the original versions of all these lists, with the exception of Beers Criteria®, of which we have studied the 2019 version.

For all lists, when a specific dosing was mentioned for any explicit criteria, it was not taken into consideration; the drug concerned was considered as a PIM exposure regardless of how it was taken. In our study, a PIM exposure was defined as an index admission with an FRI that had at least one PIM at hospital discharge.

2.4) Measures

The primary outcome was the proportion of patients with 30-day all-cause unplanned hospital readmission to one of the 11 hospitals in the study. Data were extracted at the index admission of FRI and the analyzed variables included: demographic characteristics (age, gender), admission characteristics (entry mode, length of stay and previous hospital admission in the 6 months prior to the index admission), therapeutic characteristics (prescribed drugs presented in the Anatomical Therapeutic Classification (ATC), presence of PIM defined by the selected lists), diagnosis characteristics (according to the ICD-10, number of comorbidities and Charlson index based on the algorithm developed by *Quan et al.*[21]). The C-Reactive Protein (CRP) test results were also analysed. According to the significance of the clinical interpretation, this variable was categorized according to normal clinical rates.

2.5) Statistical Analysis

A descriptive analysis of the study population was performed. Baseline characteristics were described by mean and standard deviation for continuous variables and numbers and percentages for qualitative variables. We used a t-test to compare means for quantitative variables and Chi-squared test to compare the percentages of qualitative variables between the following two groups: exposed and non-exposed to PIMs for all six lists.

To reduce potential selection bias, Propensity Score Matching (PSM) was performed. Propensity scores were estimated using logistic regressions where the number of PIMs of each list was regressed on the following covariates: male gender, abnormal concentration of C-reactive protein (CRP), anemia, malignant tumor, traumatic injury, previous hospital admission (6 months before index admission) and length of stay. These

covariates were risk factors of hospital readmission after an FRI that were identified previously.[22] PSM created two comparable groups on all observed covariates except for the presence of PIMs. We examined each list of PIMs in separate analyses. Covariate balance was assessed by examining the standardized mean differences (SMD) for each covariate. A threshold of 0.2 was used to indicate good balance.

We selected the propensity score subclassification method with 6 subclasses for the lists. After matching, most standardized mean differences for the covariates were below 0.2. For the ones that were slightly above 0.2, an adjustment for double robustness was made. No units were discarded by the matching.

To estimate the effect of PIM exposure from each list on readmissions, we fitted logistic regression models with the PIM list as the sole predictor in each of the 6 propensity score matched samples. The coefficients were exponentiated to odds ratios for ease of interpretation. Statistical significance was two-tailed and set at $p<0.05$.

Continuous secondary outcomes were analyzed using linear model analysis. Odds-Ratio (OR) and 95% Confidence Intervals (95% CI) were provided. All p values <0.05 were taken as statistically significant.

We carried out a sensitivity analysis by comparing OR obtained in full case analysis and after median imputation of missing CRP data.

All statistical analyzes were performed using R studio, Version 1.2.5001.

3) RESULTS

3.1) Study Population

From January 1st to December 31st 2019**,** a total of 670 hospital admissions met our definition of index admission with an FRI (Figure 1). Patients' mean age was 86.1 ± 6.0 years; 62.1% were women and 66.6% came directly from home. Concerning diagnosis characteristics, the mean number of comorbidities was 6.7 ± 3.5. The mean number of prescribed drugs was 13.3 ± 7.2 and 88.1% of patients were polymedicated (> 5 drugs) (Table 1).

3.2) Comparison of exposed and un-exposed to PIM groups

Overall 35.2 % of patients were exposed to a PIM according to the NORGEP criteria, 44.5 % according to PRISCUS, 46.4 % according to the Austrian consensus panel list, 51.2 % according to the French Laroche list, 72.1 % according to the EU-7 list and 85.4 % according to the Beers Criteria®.

We compared demographic, diagnosis, laboratory analysis and admission characteristics between exposed and non-exposed group of each PIM list. Table S2 shows the different results of each single list. The two variables, length of stay and abnormal concentration of CRP differed significantly between exposed and non-exposed patients in each single list. Before propensity score matching, the two groups differed in terms of the most characteristics. Good balance was achieved after matching and both groups had generaly similar distribution of all characteristics.

There were missing data for 96 (14%) admissions regarding CRP laboratory tests.

3.3) 30-Day all-cause hospital readmission

Among admissions, 19 % having at least one PIM according to Beers Criteria® and the Austrian list were readmitted within 30 days. Around 20 % of index admissions having PIMs according to the NORGEP critera and EU-7 lists resulted in 30-day hospital readmissions and around 22 % of admissions having PIMs according to the French Laroche list and PRISCUS were readmitted. After adjusting using propensity score matching, taking a PIM as per Laroche and PRISCUS lists was associated with a 30-day hospital readmission with an OR of 1.58 (95 % CI [1.06-2.37]) and 1.68 (95 % CI [1.13-2.50]) respectively while with the other 4 lists, no association was evidenced (Table 2).

3.4) Secondary Objectives

Lansoprazole was found to be the most common medication defined as a PIM in our study population according to Beers Criteria® and the EU-7 list (N=260, 38.8%). Oxazepam was the most common one according to the PRISCUS list, the NORGEP criteria, the Austrian consensus panel list and the French Laroche list (N= 130, 19.4 %). However, there was no statistically significant association between lansoprazole or oxazepam and 30-day readmission (p-value = 0.9 and 0.6, respectively). The number of PIMs according to the lists under study was not found to be associated with the time to readmissions (Table S4). After propensity score matching, being exposed to a PIM according to lists studied was not associated with a 7-day hospital readmission (Table S5).

3.5) Sensitivity Analysis

To ensure that missing data did not affect our OR estimates, we performed a median imputation of missing data. The only missing data we had were some CRP laboratory results. Missing CRP values were replaced by the median and thus all were categorized as "abnormal". After evaluation of each PIM list in a separate propensity score matched cohort, the OR estimates resembled the main findings indicating an association between exposure to a PIM according to the French Laroche and PRISCUS lists and 30-day all-cause hospital readmission. Table S6 in the supplementary files shows the results of our sensitivity analysis.

4) DISCUSSION

The aim of this study was to determine if the exposure to a PIM according to diverse lists could be associated with all cause hospital readmission after an index admission with an FRI. The French Laroche list and the PRISCUS list were both associated with an increased risk of getting readmitted to the hospital after an FRI. None of the studied lists, Beers Criteria®, NORGEP criteria, the Austrian consensus panel List and EU-7 showed any association with our primary outcome. Our findings suggest that selecting the right PIM list for adapting patient treatment after an FRI might prevent hospital readmissions within 30 days.

We did not find any association between the Beers Criteria® and hospital readmission. Interestingly, a prospective observational study conducted in Japan, having a similar case mix to that of our study, did not show any association between having a PIM according to the Beers Criteria® and unplanned hospital readmission (OR 0.93; 95% CI [0.46-1.87] and OR 0.78; 95% CI [0.36-1.66] after adjustment)[23].

In a recently published article by Guillot *et al*., based on French National Insurance databases in 2016, 64.8 % to 88.7 % of the French population had at least one chronic PIM according to a combination of the Beers Criteria® and the French Laroche list. In addition, the prevalence of PIMs according to the Beers Criteria® in a Chinese population was around 69 % [24]. Compared to our study, where 51.2 % and 85.4 % had at least one PIM according to the French Laroche list and the Beers Criteria® respectively, these results show a similarity between these study populations, estimating a high prevalence of PIMs [24,25]. However, our results concerning exposure to PIMs seem inconsistent with a study that was based on the Swedish Prescribed Drugs

Register, with a population aged 65 years and over. The prevalence of PIM was 16 %, 18 %, 19 % and 24 % according to the NORGEP criteria, the PRISCUS list, the French Laroche list and the Beers Criteria® respectively in a recent study by Morin *et al*. [26]. Our results show the same tendency but with much higher prevalence (NORGEP 35.2 %, PRISCUS 44.5%, Laroche 51.2 % and Beers Criteria® 85.4 %). This might be due to the fact that the Morin *et al.* study did not take into consideration criteria involving the disease or the clinical conditions of the individuals. The higher prevalence can also be explained with the higher age of our population.

The two most common PIMs that were identified in our study population were lansoprazole, a Proton Pump Inhibitor (PPI), and oxazepam, a short-to-intermediate acting benzodiazepine, with a prevalence of 38.8 % and 19.4 % respectively. These results are consistent with the article published by Guillot *et al*. In the latter study, PPIs were found to be the most chronic PIMs among older adults of a French population with a prevalence between 43.4 % and 67.1 %, followed by short and intermediate-acting benzodiazepines (between 13.7 % and 23 %) based on Beers Criteria® and the French Laroche list of PIMs combined [25]. In addition, Morin *et al*., found that benzodiazepines and benzodiazepines-like drugs were the most common PIM in a Swedish sample of population [26]. According to Chang and Chan, short acting benzodiazepines were associated with FRIs [8].

Our results show that the number of PIMs is not associated with in the time to readmission. This would imply that interventions to decrease hospital readmission should be targeted at suppressing all PIMs and not only minimizing their number.

This study has limitations that should be considered when interpreting the results. First, all PIM lists, except for the Austrian one, included some dosing specification when defining a certain drug being a PIM. For instance, the French Laroche list comprised dosing specifications for benzodiazepines, where the drug concerned would be considered as a PIM if it exceeded a certain daily dose. Due to the way data was collected, it was not feasible to take into consideration these specifications. Therefore, the mentioned benzodiazepines were all considered to be PIMs regardless of how our study population took those drugs. However, as all lists include dosing specification, the two lists identified in our study seem to be relevant. Secondly, our study population included 670 admissions and 579 patients. Therefore, some patients were included more than once in the analysis and if they were using any PIMs, they were counted twice because they were considered as two hospital admissions

with an FRI. Thirdly, it was not possible to know if patients were compliant with their medications after discharge and if they had any new prescriptions during the 30-day follow up period. Forthly, we could not identify which PIM(s) may be associated with an increased hospital readmission. However, as we showed that PIMs increase the risk of readmission, regardless of the number in a single prescription, an effort should be made to suppress all of them, whatever the drug. Fifthly, due to the fact that we used a CDW, we could only compare explicit lists, thus excluding the STOPP and START list which is widely used.

Finally, this study was multicenter and thus the results may be generalizable to the French population with an index admission with an FRI.

The relation between PIM prescription and ADE (i.e., hospital admission or readmission) has been widely described in the literature. Our study evidenced that not all lists published allow the accurate prediction of hospital readmissions to the same extent. We found that PIMs defined using the French Laroche and PRISCUS lists were associated with increased 30-day all-cause hospital readmissions after an FRI contrary to theBeers Criteria®, the NORGEP criteria, the Austrian consensus panel list, and EU-7 that did not evidence any association with readmission, our primary outcome.

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FIGURE LEGEND

Fig. 1 **Flow diagram**

FRI: Falls and related injuries

TABLES

Table 1: Patient characteristics at index admission with an FRI

Characteristics	**Admissions (N = 670)**
Age (years), mean ± SD	86.1 ± 6.1
Gender, n (%)	
Female	416 (62.1)
Male	254 (37.9)
Entry mode, n (%)	
Home	446 (66.6)
Other	224 (33.4)
Number of comorbidites, mean ± SD	6.7 ± 3.5
Number of drugs, mean ± SD	13.28 ± 7.19
Polymedication (>5 drugs), n (%)	590 (88.1)

Table 2: Adjusted Odd Ratios (95% CIs) of 30-day All-cause Hospital Readmission by PIM exposure

Variable[1]	OR	95% CI	p-value[2]
PIMs according to the Beers Criteria®	1.32	[0.75-2.50]	0.36
PIMs according to the french Laroche list	1.58	[1.06-2.37]	*0.025*
PIMs according to the NORGEP Criteria	1.38	[0.91-2.07]	0.13
PIMs according to The PRISCUS list	1.68	[1.13-2.50]	*0.01*
PIMs according to the Austrian consensus panel list	1.10	[0.77-1.71]	0.21
PIMs according to The EU(7)-PIM list	1.34	[0.86-2.13]	0.44

[1] Each PIM list was evaluated in a separate propensity-score matched cohort based on the PIM list type

[2] All p-values <0.05 were considered statistically significant.

Table S1: ICD-10 codes for FRIs

Fall or an associated diagnosis	
Tendency to fall, not elsewhere classified	R29.6
Other and unspecified abnormalities of gait and mobility	R26.8
Difficulty in walking, not elsewhere classified	R26.2
Unspecified fall	W19.0
Fracture of neck of femur	S72.00
Other	H82, R42, S00, S40, S50, S60, S70, S7210, S72, S80, S83, W01, W10, W18, W19

Table S2: Comparison between exposed and non-exposed to PIM of each studied PIM list

Characteristics	Beers Non-exposed N = 98	Beers Exposed N = 572	p-value	Laroche Non-exposed N=327	Laroche Exposed N=343	p-value	Norgep Non-exposed N=434	Norgep Exposed N=236	p-value
Demographic characteristics									
Gender, n (%)			0.761			0.005			0.097
Female	59 (60.2)	357 (62.4)		185 (56.6)	231 (67.3)		259 (59.7)	157 (66.5)	
Age (years), mean ± SD	88.12 ± 5.84	85.77 ± 6.02	<0.001	86.44 ± 6.18	85.81 ± 5.92	0.174	86.18 ± 6.04	86.00 ± 6.09	0.710
Diagnostic characteristics									
Anemia, n (%)	10 (10.2)	122 (21.3)	0.015	50 (15.3)	82 (23.9)	0.007	81 (18.7)	51 (21.6)	0.415
Traumatic injury, n (%)	48 (49.0)	207 (36.2)	0.022	130 (39.8)	125 (36.4)	0.422	154 (35.5)	101 (42.8)	0.075
Malignant tumor, n (%)	9 (9.2)	77 (13.5)	0.314	36 (11.0)	50 (14.6)	0.206	53 (12.2)	33 (14.0)	0.594
Laboratory analysis characteristics									
Abnormal concentration of CRP, n (%)	34 (34.7)	362 (63.3)	<0.001	169 (51.7)	227 (66.2)	<0.001	239 (55.1)	157 (66.5)	<0.001
Admission characteristics									
Length of stay, mean ± SD	11.43 ± 16.80	25.67 ± 30.53	<0.001	18.69 ± 22.18	28.25 ± 34.24	<0.001	19.69 ± 23.89	30.75 ± 36.36	<0.001
Previous hospital admission (6 months before index admission), n (%)	35 (35.7)	183 (32.0)	0.542	114 (34.9)	104 (30.3)	0.241	144 (33.2)	74 (31.4)	0.693

Characteristics	Priscus Non-exposed N=372	Priscus Exposed N=298	p-value	Austria Non-exposed N = 359	Austria Exposed N = 311	p-value	EU-7 Non-exposed N=188	EU-7 Exposed N=482	p-value
Demographic characteristics									
Gender, n (%)			0.066			0.133			0.567
Female	219 (58.9)	197 (66.1)		213 (59.3)	203 (65.3)		113 (60.1)	303 (62.9)	
Age (years), mean ± SD	86.54 ± 6.10	85.59 ± 5.96	0.042	86.52 ± 5.98	85.66 ± 6.11	0.066	87.40 ± 6.22	85.62 ± 5.91	0.001
Diagnostic characteristics									
Anemia, n (%)	60 (16.1)	72 (24.2)	0.012	63 (17.5)	69 (22.2)	0.159	26 (13.8)	106 (22.0)	0.023
Traumatic injury, n (%)	144 (38.7)	111 (37.2)	0.759	138 (38.4)	117 (37.6)	0.890	86 (45.7)	169 (35.1)	0.014
Malignant tumor, n (%)	46 (12.4)	40 (13.4)	0.772	41 (11.4)	45 (14.5)	0.289	19 (10.1)	67 (13.9)	0.234
Laboratory analysis characteristics									
Abnormal concentration of CRP, n (%)	197 (53.0)	199 (66.8)	<0.001	196 (54.6)	200 (64.3)	<0.001	86 (45.7)	310 (64.3)	<0.001
Admission characteristics									
Length of stay, mean ± SD	20.26 ± 25.21	27.73 ± 33.42	0.001	19.47 ± 24.34	28.34 ± 33.67	<0.001	17.80 ± 23.95	25.84 ± 30.95	0.001
Previous hospital admission (6 months before index admission), n (%)	126 (33.9)	92 (30.9)	0.459	125 (34.8)	93 (29.9)	0.203	64 (34.0)	154 (32.0)	0.669

Table S3: Unadjusted Odd Ratios (95% CIs) of 30-day All-cause Hospital Readmission by PIM exposure

Variable	OR	95% CI	p-value*
PIMs according to the Beers Criteria®	0.97	[0.57-1.71]	0.91
PIMs according to the french Laroche list	1.42	[0.96-2.11]	0.077
PIMs according to the NORGEP Criteria	1.15	[0.77-1.71]	0.5
PIMs according to The PRISCUS list	1.51	[1.02-2.23]	0.038
PIMs according to the Austrian consensus panel list	1.00	[0.68-1.50]	0.99
PIMs according to The EU(7)-PIM list	1.30	[0.81-1.99]	0.31

Each PIM list was evaluated in a separate propensity-score matched cohort based on the PIM list type
All p-values <0.05 were considered statistically significant.

Table S4: Number of PIMs and delay in hospital readmission

Variable	OR	CI	p-value*
Number of PIMs according to the Beers Criteria®	1.00	[0.89-1.20]	0.75
Number of PIMs according to the french Laroche list	1.30	[0.91-2.00]	0.14
Number of PIMs according to the NORGEP Criteria	1.00	[0.57-1.80]	0.99
Number of PIMs according to The PRISCUS list	1.60	[0.90-2.60]	0.11
Number of PIMs according to the Austrian consensus panel list	1.00	[0.60-1.80]	0.89
Number of PIMs according to The EU(7)-PIM list	1.10	[0.81-1.60]	0.48

Table S5: Adjusted Odd Ratios (95% CIs) of 7-day All-cause Hospital Readmission by PIM exposure

Variable	OR	CI	p-value*
PIMs according to the Beers Criteria®	0.75	[0.31-1.60]	0.50
PIMs according to the french Laroche list	0.81	[0.48-1.40]	0.43
PIMs according to the NORGEP Criteria	0.89	[0.52-1.60]	0.69
PIMs according to The PRISCUS list	0.80	[0.47-1.40]	0.42
PIMs according to the Austrian consensus panel list	0.96	[0.57-1.60]	0.88
PIMs according to The EU(7)-PIM list	1.10	[0.60-1.90]	0.78

Each PIM list was evaluated in a separate propensity-score matched cohort based on the PIM list type
All p-values <0.05 were considered statistically significant.

Table S6: Adjusted ORs (95% CIs) of 30-day All-cause Hospital Readmission by PIM exposure after median imputation

Variable	OR	CI	p-value*
PIMs according to the Beers Criteria®	1.22	[0.70-2.25]	0.50
PIMs according to the french Laroche list	1.62	[1.09-2.43]	0.019
PIMs according to the NORGEP Criteria	1.38	[0.91-2.08]	0.12
PIMs according to The PRISCUS list	1.83	[1.22-2.74]	0.0034
PIMs according to the Austrian consensus panel list	1.2	[0.79-1.74]	0.44
PIMs according to The EU(7)-PIM list	1.31	[0.84-2.08]	0.24

Each PIM list was evaluated in a separate propensity-score matched cohort based on the PIM list type
All p-values <0.05 were considered statistically significant.

Table S7: RECORD statement for pharmacoepidemiology (RECORD-PE) checklist

Item No	STROBE items	RECORD items	RECORD-PE items	Page No
Title and abstract				
1	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was done and what was found.	1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. 1.2: If applicable, the geographical region and timeframe within which the study took place should be reported in the title or abstract. 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	—	1
Introduction				
Background rationale				
2	Explain the scientific background and rationale for the investigation being reported.	—	—	2-3
Objectives				
3	State specific objectives, including any prespecified hypotheses.	—	—	3
Methods				
Study design				
4	Present key elements of study design early in the paper.	—	4.a: Include details of the specific study design (and its features) and report the use of multiple designs if used. 4.b: The use of a diagram(s) is recommended to illustrate key aspects of the study design(s), including exposure, washout, lag and observation periods, and covariate definitions as relevant.	3
Setting				

5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.	—	—	3-4
Participants				
6	(a) Cohort study—give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. Case-control study—give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. Cross sectional study—give the eligibility criteria, and the sources and methods of selection of participants. (b) Cohort study—for matched studies, give matching criteria and number of exposed and unexposed. Case-control study—for matched studies, give matching criteria and the number of controls per case.	6.1: The methods of study population selection (such as codes or algorithms used to identify participants) should be listed in detail. If this is not possible, an explanation should be provided. 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	6.1.a: Describe the study entry criteria and the order in which these criteria were applied to identify the study population. Specify whether only users with a specific indication were included and whether patients were allowed to enter the study population once or if multiple entries were permitted. See explanatory document for guidance related to matched designs.	3-5
Variables				
7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	7.1.a: Describe how the drug exposure definition was developed. 7.1.b: Specify the data sources from which drug exposure information for individuals was obtained. 7.1.c: Describe the time window(s) during which an individual is considered exposed to the drug(s). The rationale for selecting a particular time window should be provided. The extent of potential left truncation or left censoring should be specified. 7.1.d: Justify how events are attributed to current, prior, ever, or cumulative drug exposure.	4-5

			7.1.e: When examining drug dose and risk attribution, describe how current, historical or time on therapy are considered. 7.1.f: Use of any comparator groups should be outlined and justified. 7.1.g: Outline the approach used to handle individuals with more than one relevant drug exposure during the study period.	
Data sources/measurement				
8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.	—	8.a: Describe the healthcare system and mechanisms for generating the drug exposure records. Specify the care setting in which the drug(s) of interest was prescribed.	4-5
Bias				
9	Describe any efforts to address potential sources of bias.	—	—	5
Study size				
10	Explain how the study size was arrived at.	—	—	Figure 1
Quantitative variables				
11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why.	—	—	5-6
Statistical methods				
12	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) Cohort study—if applicable, explain how loss to follow-up was addressed. Case-control study—if applicable, explain how matching of cases and controls was addressed. Cross sectional study—if applicable, describe analytical methods taking account of sampling strategy. (e) Describe any sensitivity analyses.	—	12.1.a: Describe the methods used to evaluate whether the assumptions have been met. 12.1.b: Describe and justify the use of multiple designs, design features, or analytical approaches.	5-6
Data access and cleaning methods				

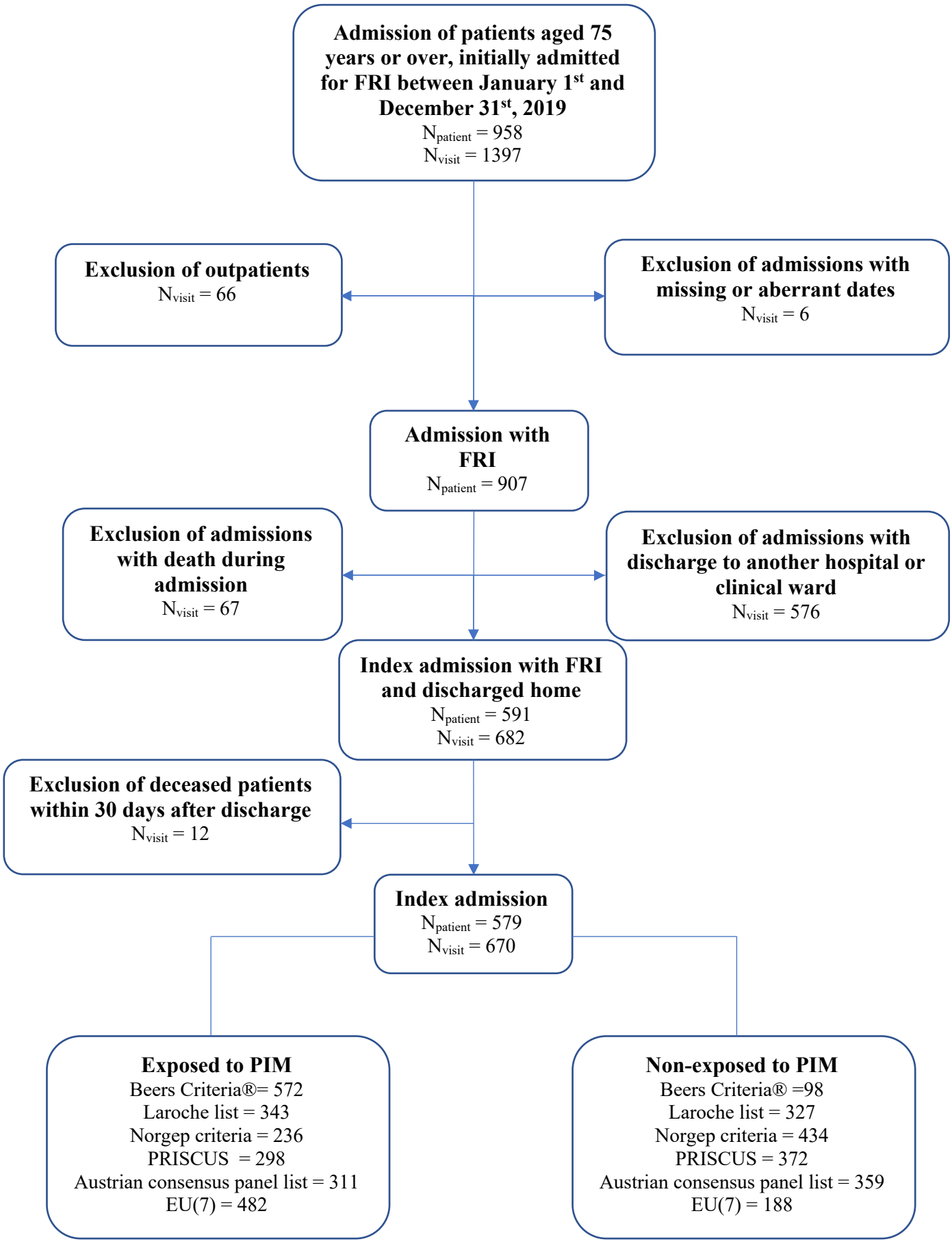
12	—	12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. 12.2: Authors should provide information on the data cleaning methods used in the study.	—	3-5
Linkage				
12	—	12.3: State whether the study included person level, institutional level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	—	3-5
Results				
Participants				
13	(a) Report the numbers of individuals at each stage of the study (eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed). (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram.	13.1: Describe in detail the selection of the individuals included in the study (that is, study population selection) including filtering based on data quality, data availability, and linkage. The selection of included individuals can be described in the text or by means of the study flow diagram.	—	Figure 1
Descriptive data				
14	(a) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders. (b) Indicate the number of participants with missing data for each variable of interest. (c) Cohort study—summarise follow-up time (eg, average and total amount).	—	—	6-7 Table 1
Outcome data				
15	Cohort study—report numbers of outcome events or summary measures over time. Case-control study—report numbers in each exposure category, or summary measures of exposure.	—	—	7

	Cross sectional study—report numbers of outcome events or summary measures.			
Main results				
16	(a) Give unadjusted estimates and, if applicable, confounder adjusted estimates and their precision (eg, 95% confidence intervals). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables are categorised. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.	—	—	7 Table 2 Table S2
Other analyses				
17	Report other analyses done—eg, analyses of subgroups and interactions, and sensitivity analyses.	—	—	8
Discussion				
Key results				
18	Summarise key results with reference to study objectives.	—	—	8
Limitations				
19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	19.1.a: Describe the degree to which the chosen database(s) adequately captures the drug exposure(s) of interest.	9-10
Interpretation				
20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	—	20.a: Discuss the potential for confounding by indication, contraindication or disease severity or selection bias (healthy adherer/sick stopper) as alternative explanations for the study findings when relevant. **[A: Original text indicated this item was RECORD (ie, not RECORD-PE)?]**	8-10

Generalisability				
21	Discuss the generalisability (external validity) of the study results.	—	—	9
Other information				
Funding				
22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.	—	—	-
Accessibility of protocol, raw data, and programming code				
22	—	22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	—	-

RECORD=reporting of studies conducted using observational routinely collected data; RECORD-PE=RECORD for pharmacoepidemiological research; STROBE=strengthening the reporting of observational studies in epidemiology.

*REFERENCE: Langan SM, Schmidt S, Wing K, Ehrenstein V, Nicholls S, Filion K, Klungel O, Petersen I, Sorensen H, Guttmann A, Harron K, Hemkens L, Moher D, Schneeweiss S, Smeeth L, Sturkenboom M, von Elm E, Wang S, Benchimol EI. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement for Pharmacoepidemiology (RECORD-PE). *BMJ* 2018; 363: k3532.


Admission of patients aged 75 years or over, initially admitted for FRI between January 1st and December 31st, 2019
Npatient = 958
Nvisit = 1397
Exclusion of outpatients
Nvisit = 66
Exclusion of admissions with missing or aberrant dates
Nvisit = 6
Admission with FRI
Npatient = 907
Exclusion of admissions with death during admission
Nvisit = 67
Exclusion of admissions with discharge to another hospital or clinical ward
Nvisit = 576
Index admission with FRI and discharged home
Npatient = 591
Nvisit = 682
Exclusion of deceased patients within 30 days after discharge
Nvisit = 12
Index admission
Npatient = 579
Nvisit = 670
Exposed to PIM
Beers Criteria®= 572
Laroche list = 343
Norgep criteria = 236
PRISCUS = 298
Austrian consensus panel list = 311
EU(7) = 482
Non-exposed to PIM
Beers Criteria® =98
Laroche list = 327
Norgep criteria = 434
PRISCUS = 372
Austrian consensus panel list = 359
EU(7) = 188