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ORIGINAL ARTICLE

Potentially Inappropriate Medication Use in Older Adults with Chronic Kidney Disease

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ABSTRACT

Objectives: This study aimed to identify the prevalence of potentially inappropriate medication use (PIMU) in adults above the age of 65 with chronic kidney disease (CKD) according to the American Geriatric Society Beers Criteria (Beers), Screening Tool of Older People's Potentially Inappropriate Prescriptions Criteria (STOPP) and medication appropriateness index (MAI) 30 criteria and to compare them to justify their use in this specific patient group.

Materials and Methods: This was a retrospective and descriptive study conducted between October 1st, 2019 and March 18th, 2020 at Ibni Sina Hospital, Nephrology Department, Faculty of Medicine, Ankara University.

Results: Among 269 patients discharged from the hospital during the study period, 100 of them were eligible for the study. The mean age was 73.3 ± 6.9 years and 51.9% of them were male. The prevalence of 35 PIMU was 91%, 42%, and 70% according to the Beers, STOPP, and MAI criteria, respectively. There was a statistically significant difference in terms of prevalence among 3 criteria (p<0.001). Beer detected more PIMU (11.3% *vs.* 6.4%) and had higher sensitivity among older adults with CKD (0.97 *vs.* 0.56) compared to the STOPP criteria. Most patients had at least one drug-drug interaction (DDIs) in their discharge prescription (93%) and DDI was one of the main contributors of PIMU. Proton pump inhibitors were the most common medication associated with PIMU in all 3 criteria.

Conclusion: The prevalence of PIMU was high among older adults with CKD at discharge according to these criteria. To improve the prescriptions after hospital discharge, it is considered appropriate to use Beers criteria under guidance of a clinical pharmacist.

Key words: Potentially inappropriate medication use, older adults, chronic kidney disease

INTRODUCTION

Number of elderly people has been increasing gradually in recent decades. It is estimated to reach 1.5 billion by 2050 in both developing and developed countries.[1] In Türkiye, the average life expectancy is projected to be 82.5 and 89.1 years in 2050 and 2100, respectively.[2] As life expectancy increases, number of older adults in the population increases, thus causing a high number of people with many comorbidities. Due to comorbidities, older adults take many medications that make them prone to potentially inappropriate medication use (PIMU). PIMU can cause undesirable consequences, such as adverse drug reactions, hospital admissions/readmissions, increased treatment costs, morbidity, and mortality.[3,4]

Chronic kidney disease (CKD) is one of the most common comorbidities seen in older adults.[5] This is mainly due to the traditional risk factors for CKD, including cardiovascular disease, hypertension, and diabetes.[5] The prevalence of CKD in older adults in Türkiye is 5% (age ≥60 years), while it is 4.1% (age 65-74) in Switzerland, 25.4% (age 65-74) in northeast Germany and 39.4% (age >60 years) in the United States of America (USA).[5-7] A systematic review, which included 10 studies from USA, 8 studies from Europe, and 8 studies from Asia and Australia, found that the prevalence of CKD among older adults ranged from 23.4% to 35.8% (age ≥64 years).[8] Physiological changes caused by aging and decreased kidney function in older adults with CKD affect pharmacokinetic

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and pharmacodynamic properties of medicines, leading to various problems in absorption, metabolism, distribution, and elimination stages.[9,10] These problems can alter the effectiveness of medications or increase the frequency of side effects or toxicities. Therefore, PIMU is often observed in older adults with CKD and is estimated to be 62-67% in the hospital and ambulatory care settings.[4,9,10]

Several screening tools have been developed to improve medication use among older adults. These tools for elderly patients are classified as explicit implicit. Explicit tools are usually developed from published reviews, expert opinions, and consensus reports. These tools are mostly drug-specific and/or disease-specific and can be applied with little or no clinical judgment.[11] The commonly used tools in practice are as follows: The American Geriatric Society Beers criteria (Beers criteria), Screening Tool of Older People's Potentially Inappropriate Prescriptions Criteria (STOPP).[12,13] Implicit tools are judgement-based, patient-specific, and consider the patient's entire medication regimen. Implicit criteria are based on the pharmacist's and/or geriatrics' knowledge, experience, and attitude.[11] Medication appropriateness index (MAI) is an implicit screening tool.[14] These tools provide useful information about what can be potentially inappropriate, when prescribed for older adults.[15,16] They are also widely and easily implemented in many healthcare settings.[15,16]

Discharge from the hospital can put patients at a high risk, when they are prescribed new medications or do not receive any counseling about the appropriate use of medications. Pharmacists can provide medication review services at discharge to identify PIMU for patients, particularly older adults with CKD taking many medicines. This service is crucial for them because they are known to require dose adjustments based on the glomerular filtration rate (GFR), polypharmacy, comorbidities, and age-related physiological changes. There are limited data on the frequency of PIMU among older adults with CKD. Therefore, the primary aim of this study was to describe PIMU among older adults with CKD by using the Beers, STOPP, and MAI criteria. The secondary aim was to compare these criteria in terms of their identifiability, sensitivity, and specificity for PIMU among patients with CKD by examining discharge prescriptions.

MATERIALS AND METHODS

Study design and setting

This descriptive cross-sectional study was conducted between October 1st, 2019 and March 18th, 2020 at Ibni Sina Hospital, Nephrology Department, Faculty of Medicine, Ankara University. Ibni Sina Hospital is a 1,000-bed, government-run tertiary university hospital in Türkiye. The nephrology ward accepts patients mainly from Ankara, but a considerable number of patients are admitted to the ward, as it is one of the largest university hospitals in Türkiye. This ward has 34-bed and patients are followed up by 6 physicians and 7 nurses, however, there is no clinical pharmacist.

Ethics approval

The study was approved by the Ethics Committee for Human Research of the Ankara University Faculty of Medicine (date: September 12, 2019; no: İ3-70-19).

Data collection

Patients who were discharged from the nephrology ward during the study period were screened using their electronic discharge notes. Patients, who were 65 years old or older, discharged from the nephrology service and diagnosed with CKD, were considered eligible (the classification of kidney function was based on the Kidney Disease Improving Global Outcomes-KDIGO guidelines in this study). Patients discharged due to transfer to another hospital or service were excluded from the study.

A data collection form was used to obtain patients' admission diagnosis, length of stay, age, sex, and list of medications during discharge. All information was retrospectively gathered from the electronic medical records of all eligible patients. Detailed information regarding the patients' admission diagnoses and prescription medications was also collected. Prescription records included names, therapeutic classes, doses, dosage forms, and dosage regimens of the prescribed medications.

Evaluating potentially inappropriate medication use

To identify PIMU at discharge, 3 criteria were used: Beers,[12] STOPP,[16] and MAI.[14]

Beers criterion was developed by American Geriatric Society.[12] The recent Beers criteria published in 2019 include the following 5 categories for PIMU:[12]

1. PIMU: In older adults,
2. PIMU due to drug-disease/syndrome interactions that exacerbate the disease/syndrome,
3. PIM to be used with caution,
4. Potentially clinically important drug-drug interactions (DDIs) that should be avoided,
5. Medication that should be avoided or have reduced dosage with varying levels of kidney function.

STOPP criteria were developed by O'Mahony et al.[16] It consists of a section related to the indication of medications that might be prescribed without an evidence-based clinical indication, prescribed beyond the recommended duration, although the treatment duration is well-defined or duplicated.[16] Other sections consist of criteria for each medication group such as cardiovascular system medications and gastrointestinal system medications.[16]

MAI includes 10 parameters such as indication (1), effectiveness (2), dosage (3), correct directions (4), practical directions (5), DDIs (6), drug-disease interactions (7), duplications (8), durations (9), and expenses (10).[14] The scoring of MAI uses a different process from the mentioned tools. This tool requires the user to answer 10 questions regarding a particular medication to determine its appropriateness for a patient. All "yes" responses have a score of zero, while "no" responses have values ranging from 1 to 3 depending on their importance in assessing the appropriateness

of a particular drug. The maximum score of 18 is interpreted as a maximum inappropriateness.[14] In patients' discharge records, it was not stated whether the correct and practical instructions were given to them.[14] All equivalent medications are likely to have the same price in Türkiye.[17] Therefore, these 3 parameters of MAI were not scored.

Lexicomp® drug interaction checker was used to identify DDIs.[18] DDIs were classified as categories A, B, C, D, and X according to Lexicomp®.[18] DDIs belonging to categories D and X were assumed to be clinically important interactions present in the MAI, whereas DDIs belonging to categories A, B, and C were assumed to be minor interactions present in the MAI.

PIMU is defined by the pharmacist as occurring when a medication was categorized as inappropriately used according to Beers, STOPP or MAI.

Comparison between Beers, STOPP and MAI criteria

The tools were compared based on the frequency of detected PIMU among the study population. Sensitivity and specificity were calculated according to the optimal cut-off value. MAI criteria were selected as a reference since their reliability and validity were tested in previous studies.[14,15,19]

Statistical analysis

Categorical variables were described with percentages, and continuous variables were described with the mean ± standard deviation (SD). The chi-square test was used, and a p value <0.05 was considered statistically significant. The degree of agreement was determined using the Kappa statistic. A receiver operating characteristic (ROC) curve was used to estimate the areas under the ROC curves. Data were analyzed using SPSS version 21.0 (IBM SPSS Statistics for Windows, Version 21.0; IBM Corp., Armonk, NY, USA). Microsoft Excel for Windows version 2016 was used to calculate PIMs, prevalence, and medication usage rates.

RESULTS

Demographic and clinical characteristics of the patients

During the study period, 269 patients were discharged from the nephrology ward. Among these, patients were excluded, if they were younger than 65 years (n= 154), died before discharge (n= 3), discharged without any prescription (n= 8) or were transferred to another hospital/ward (n= 4) (Figure 1).

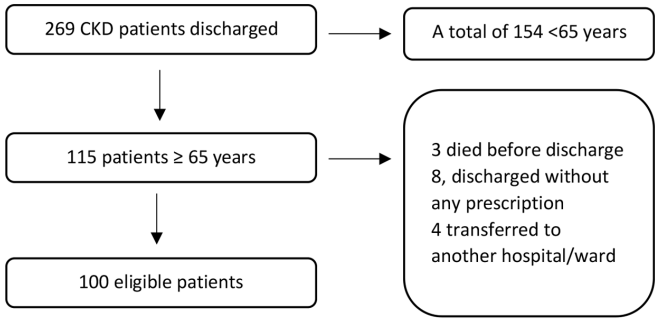

Figure 1. Selection of the patients

In total, 100 patients (mean ± SD age, 73.3 ± 6.9 years; 51.0% male) were included in the study. The most common comorbidities of the patients were hypertension (83.0%), diabetes mellitus (57.0%), and coronary artery diseases (31.0%). Patients' duration of hospital stay (mean ± SD) was 10.7 ± 7.4. The number of comorbidities and medications (mean ± SD) between the patients were 3.6 ± 1.3 and 9.4 ± 3.2, respectively. The percentages of patients based on CKD stages 1, 2, 3, 4, and 5 were 3.0%, 10%, 33%, 38%, and 18%, respectively. Patients' hemoglobin levels (mean ± SD) were low (10.7 ± 1.9 g/dL), while serum uric acid (7.6 ± 0.2 mg/dL) and parathormone levels were high (166.3 ± 141.2 pg/mL) according to KDIGO guidelines (Table 1).

A total of 928 medications were prescribed. The most commonly prescribed medication classes were for cardiovascular system (35.2%), alimentary tract and metabolism (22.3%), and blood and blood-forming organs (16.7%). The most commonly used medications in this study were pantoprazole/esomeprazole/lansoprazole (65%), atorvastatin/rosuvastatin/pravastatin/pitavastatin (58%), and aspirin (49%). Among these patients, 30% were prescribed at least one oral antidiabetic agent (20% linagliptin, 9% metformin, 3% sitagliptin, 2% vildagliptin, and 1% empagliflozin).

PIMU according to the Beers criteria

Most participants were prescribed at least one PIM according to Beers criteria [91.0%, 95% confidence interval (CI): 85.0-96.0]. Among these, 31 patients (31.0%, 95% CI :22.0-40.0) received only one PIM, 40 (40.0%; 95% CI: 30.0-50.0) received two PIMs, 19 (19.0%, 95% CI: 12.0-27.0) received three PIMs, and one (6.3%; 95% CI: 0.0-3.0) received four PIMs.

Overall, 11.3% of the medications were potentially inappropriate (n= 105 out of 928) according to Beers criteria. The most common PIM classes were proton pump inhibitors (PPIs) (65%), diuretics (50%), antiplatelets/anticoagulants (31%), and alpha-1 adrenergic blockers (30%). The most common reasons for PIM were a high risk of side effects (71.4%), long duration (71.4%), and risks of the medicine outweighing the benefits (34.1%) (Table 2).

A total of 13 DDIs were identified on the basis of Beers criteria. The most common DDI was between doxazosin and furosemide (92%). However, these common DDIs were not present in the Lexicomp® drug interaction checker.

PIMU according to STOPP criteria

According to the STOPP criteria, 42 patients (42.0%; 95% CI: 33.0-52.0) were prescribed at least one PIM. Among these patients, 34 (34.0%; 95% CI: 26.0-43.0) received only one PIM, 7 (7.0%; 95% CI: 2.0-12.0) received two PIMs, and one (1.0%; 95% CI: 0.0-4.0) received three PIMs.

Overall, 6.3% of the medications were potentially inappropriate (n= 58/928) according to STOPP criteria. The most common PIM classes were PPIs (10%), psychotropic drugs (9%), and antiplatelets/anticoagulants (8%). The most common reasons for PIM were medication use without indication (78.6%), and risks of the medicine outweighing the benefits (19.0%) (Table 2).

PIMU according to MAI criteria

The mean ± SD MAI score *per* drug was 8.7 ± 1.2, while the mean ± SD MAI score *per* patient was 80.4 ± 28.9. Based on MAI, 70 patients (70.0%; 95% CI: 61.0-78.0) used at least one PIM.

Table 1. Demographic and clinical characteristics of the patients (n= 100)

Characteristics	Values
Male, n (%)	51 (51.0)
Age (years), mean ± SD	73.3 ± 6.9
Age (years), n (%)	
≥80	18 (18.0)
Number of comorbidities, mean ± SD	3.6 ± 1.3
Number of comorbidities, n (%)	
≥5	26 (26.0)
Hypertension	83 (83.0)
Diabetes mellitus	57 (57.0)
Coronary artery disease	31 (31.0)
Duration of hospital stay, mean ± SD	10.7 ± 7.4
Number of medications, mean ± SD	9.4 ± 3.2
Number of medications, n (%)	
≥5	92 (92.0)
Common medications at discharge, n (%)	
Pantoprazole/esomeprazole/lansoprazole	65 (65.0)
Atorvastatin/rosuvastatin/pravastatin/pitavastatin	58 (58.0)
Aspirin	49 (49.0)
CKD stages, n (%)	
Stage 1	3 (3.0)
Stage 2	10 (10.0)
Stage 3	33 (33.0)
Stage 4	38 (38.0)
Stage 5	18 (18.0)
Laboratory findings, mean ± SD	
Calcium (mg/dL)	8.8 ± 0.9
Phosphorus (mg/dL)	4.1 ± 1.4
Magnesium (mg/dL)	2.0 ± 0.6
Uric acid (mg/dL)	7.6 ± 0.2
Albumin (g/dL)	4.3 ± 0.7
LDL-cholesterol (mg/dL)	110.5 ± 41.5
Parathormone (pg/mL)	166.3 ± 141.2
Folic acid (ng/mL)	9.3 ± 4.7
Hb (g/dL)	10.7 ± 1.9

CKD: Chronic kidney disease, Hb: Hemoglobin, LDL: Low-density lipoprotein, SD: Standard deviation

More than a quarter of medications were rated inappropriate based on 6 criteria of MAI (25.9%). Most medications were rated inappropriate in 1-4 criteria of the MAI (92.5%). Among the medications that met at least one of MAI criteria, 51.5% were due to DDIs.

The most common PIM classes were PPIs (22%), steroids (20%), insulins (18%), oral antidiabetic drugs (14%), and antiplatelets/anticoagulants (11%). The most common reasons for PIM were DDIs (68.6%), medication use without indication (47.1%) and the need for dose adjustment for kidney function (21.4%) (Table 2).

According to the Lexicomp® drug interaction checker, most patients had at least one DDI in their discharge prescription (93%). Nearly half of the them had at least one DDI belonging to categories D or X (43%). A total of 752 DDIs were identified. The percentages of DDIs in categories A, B, C, D, and X were 0.8%, 10.5%, 78.9%, 7.9%, and 1.9%, respectively (Figure 2). Among these, the most common DDI was between aspirin and furosemide (2.8%), which belonged to category C. Information on the most common DDIs in category X and D is shown in Table 3.

Comparison of Beers, STOPP and MAI criteria

There was a statistically significant difference between the prevalence of PIMU according to Beers (91.0%), STOPP (42.0%), and MAI (70.0%) criteria (p<0.001). PIMU was more likely to be present in patients with polypharmacy (medications ≥5) according to Beers criteria (p= 0.023) (Table 2). Patients with PIMU according to MAI criteria had a longer hospital stay (p= 0.001) (Table 2). Among the patients, 39% had at least one PIM met all 3 criteria.

The most common medication group associated with potentially inappropriate use was PPIs based on all 3 criteria (65.0% *vs.* 10.0% *vs.* 22.0%). The most common reasons for PIMU varied between the criteria (Table 2).

The ROC results showed that beer had higher sensitivity than STOPP (0.97 *vs.* 0.56) and that STOPP had higher specificity than beer (0.21 *vs.* 0.46). The measures of agreement (Kappa index) were 0.26 between Beers and MAI (p<0.001) and 0.36 between STOPP and MAI (p<0.001) (Table 4). These results indicated moderate agreement between the criteria.

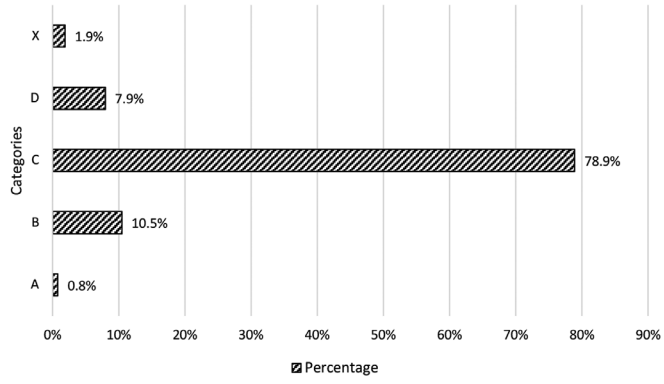

Figure 2. Percentage of drug-drug interaction categories based on Lexicomp®

Table 2. Comparison of Beers, STOPP, and MAI criteria

	Beers criteria			STOPP criteria			MAI criteria		
	Patients with PIMU, n= 91	Patients without PIMU, n= 9	*p* value	Patients with PIMU, n= 42	Patients without PIMU, n= 58	*p* value	Patients with PIMU, n= 70	Patients without PIMU, n= 30	*p* value
Gender			0.525			0.565			0.930
Male	45 (49.5)	6 (66.7)		20 (47.6)	31 (53.4)		35 (50.0)	16 (53.3)	
Female	46 (50.5)	3 (33.6)		22 (52.4)	27 (46.6)		35 (50.0)	14 (46.7)	
Number of medications			0.023			0.134			0.050
<5	5 (5.5)	3 (33.3)		1 (2.4)	7 (12.1)		3 (4.3)	5 (16.7)	
≥5	86 (94.5)	6 (66.7)		41 (97.6)	51 (87.9)		67 (95.7)	25 (83.3)	
Duration of hospital stay (mean ± SD)	10.9 ± 7.6	8.0 ± 3.9	0.255	11.7 ± 7.8	9.9 ± 7.0	0.224	11.9 ± 8.0	7.8 ± 4.5	0.001
CKD stage			1.000			0.519			0.497
Stage 1-2 (eGFR ≥60 mL/min/1.73 m^2)	10 (11.0)	1 (11.1)		6 (14.3)	5 (8.6)		9 (12.9)	2 (6.7)	
Stage 3-5 (eGFR <60 mL/min/1.73 m^2)	81 (89.0)	8 (88.9)		36 (85.7)	53 (91.4)		61 (87.1)	28 (93.3)	
Number of comorbidities			1.000			0.149			0.201
0-4	66 (72.5)	7 (77.8)		27 (64.3)	46 (79.3)		48 (68.6)	25 (83.3)	
≥5	25 (27.5)	2 (22.2)		15 (35.7)	12 (20.7)		22 (31.4)	5 (16.7)	
Common reasons for PIMU									
The risks of medicine outweigh the benefits	31 (34.1)	N/A		8 (19.0)	N/A		0 (0.0)	0 (0.0)	
High risk of side effects	65 (71.4)	N/A		0 (0.0)	N/A		0 (0.0)	0 (0.0)	
Long duration	65 (71.4)	N/A		2 (4.8)	N/A		0 (0.0)	0 (0.0)	
Need dose adjustment for kidney function	12 (13.2)	N/A		0 (0.0)	N/A		15	15 (21.4)	
Drug-drug interactions	13 (14.3)	N/A		N/A	N/A		43	48 (68.6)	
Medication use without Indications	N/A	N/A		33 (78.6)	N/A		33	33 (47.1)	
Use of duplicated medications	N/A	N/A		2 (4.8)	N/A		2	2 (2.9)	
Common medicines associated with PIMU									
Proton pomp inhibitors	65 (71.4)	N/A		10 (23.8)	N/A		22 (31.4)	N/A	
Diuretics	50 (54.9)	N/A		0 (0.0)	N/A		0 (0.0)	N/A	
Antiplatelets/anticoagulants	31 (34.1)	N/A		8 (19.0)	N/A		11 (15.7)	N/A	
Alpha-1 blockers	30 (32.9)	N/A		1 (2.4)	N/A		8 (11.4)	N/A	
Insulins	2 (2.2)	N/A		0 (0.0)	N/A		18 (25.7)	N/A	
Psychotropic drugs	10 (10.9)	N/A		9 (21.4)	N/A		7 (10.0)	N/A	
Oral antidiabetic drugs	0 (0.0)	N/A		1 (2.4)	N/A		14 (20.0)	N/A	
Steroids	0 (0.0)	N/A		0 (0.0)	N/A		20 (28.6)	N/A	

CKD: Chronic kidney disease, eGFR: Estimated glomerular filtration rate, N/A: Unavailable, PIMU: Potentially inappropriate medication use, STOPP: Screening Tool of Older People's Potentially Inappropriate Prescriptions Criteria, MAI: Medication appropriateness index, SD: Standard deviation

DISCUSSION

The results of this cross-sectional descriptive study showed that there was a high prevalence of PIMU among older adults with CKD, with the most common medication associated with PIMU being PPIs. To the best of our knowledge, this is the first study to describe the PIMU among elderly adults in Türkiye. This study included the discharge prescriptions of older patients with CKD.

In this study, the prevalence of PIMU based on Beers version 2019, STOPP, and MAI criteria was 91.0%, 42.0%, and 70.0%, respectively. The prevalence of PIMU was 48.0% and 83.3% according to Beers version 2015 and MAI, in a study including the same patient group in Australia.[20] In another study from USA, the prevalence of PIMU was 59.2% and 33.0% according to Beers version 2015 and STOPP, respectively, among the patients' last prescriptions in a nephrology ward.[21] The prevalence of aged-based PIMU was 32.7% according to both Beers version 2015 and STOPP criteria among the subcohort of patients with CKD.[4] In Lebanon, the prevalence of PIMU was 34.1% according to Beers version 2019 among patients with CKD.[22] The prevalence of PIMU was 32.0% according to STOPP criteria among patients with CKD in France.[23] Compared with these studies specific to CKD patients, our patients had a high prevalence of PIMU at discharge. The high prevalence in this study might have resulted from the lack of a clinical pharmacist to review medications at discharge. It was suggested that the most significant reduction in PIMU could be seen, when the physicians received immediate and concurrent feedback from a clinical pharmacist.[24]

In this study, the most common medications associated with PIMU therapy were PPIs, diuretics, antiplatelets/anticoagulants, alpha-1 blockers, insulins, psychotropics, and oral antidiabetic drugs. Similarly, PPIs,[25] benzodiazepines,[20] antiplatelets/anticoagulants, psychotropics,[21] antiplatelets/anticoagulants,[22] metformin and diuretics[4] were commonly observed as medications associated with PIMU in older adults with CKD. Moreover, most patients had used 5 or more medications in past studies.[4,20-22] Older adults with CKD often have a high drug burden and are at risk of polypharmacy-associated adverse outcomes.[24] Identification of PIMU is critical in this patient group, especially at hospital discharge, where patients may no longer be under the control of healthcare professionals. Incorporating pharmacists into discharge medication reviews to identify PIMU may improve medication use.[26-29] Additionally, collaboration and good communication between nephrologists, nurses, and pharmacists are required to review the appropriateness of medication prescription.[25] Interventions to prevent PIMU in older adults with CKD should be implemented in all healthcare settings.

According to Beers criteria, use of PPIs for more than 8 weeks was not recommended due to the risk of *Clostridium difficile* infections, osteoporosis, and bone fracture.[12] The most common medicine associated with PIMU in all 3 criteria was PPIs in our study. PPIs, statins, and oral antidiabetic agents are commonly prescribed without any indication for older adults with CKD.[24] Therefore, long-term use of PPIs could also be placed under the category of "any drug prescribed without an evidence-based clinical indication" in STOPP and "no indication" in MAI criteria. The risks and benefits of PPI use should be considered during deprescribing interventions in older adults with CKD.[24] However, specific guidance for deprescribing in this patient group does not exist.[24] There is a need for future studies to assess how PPIs can be deprescribed and what the potential clinical outcomes are after discontinuation. Medication reviews, education of health professionals and the use of decision support systems were among the strategies suggested to control the use of PPIs.[28]

Table 3. The most common drug-drug interactions according to category D or X in Lexicomp®

Drug-drug interactions	Category of DDIs	Number of DDIs
Insulin glargine-linagliptin	D	8
Methylprednisolone-sodium bicarbonate	D	6
Insulin aspart-linagliptin	D	6
Calcium carbonate-methylprednisolone	D	3
Atorvastatin-fusidic acid	X	2
Insulin lispro-linagliptin	D	2
Calcium carbonate-levofloxacin	D	2
Calcium carbonate-levothyroxine	D	2
Cefuroxime-sodium bicarbonate	D	2

DDIs: Drug-drug interactions

Table 4. Sensitivity, specificity and a measure of agreement between the criteria

Variable	Beers criteria	STOPP criteria	MAI criteria
Prevalence of PIMU (95% CI)	91.0 (85.0-96.0)	42.0 (32.0-52.0)	70.0 (61.0-78.0)
AUC (95% CI, *p* value)	0.60 (0.47-0.73, $p>0.05$)	0.73 (0.63-0.83, $p<0.001$)	Reference
Sensitivity	0.97	0.56	Reference
Specificity	0.21	0.46	Reference
Kappa index (*p* value)	0.26 ($p<0.001$)	0.36 ($p<0.001$)	Reference

AUC: Area under the curve, CI: Confidence interval, PIMU: Potentially inappropriate medication use, STOPP: Screening Tool of Older People's Potentially Inappropriate Prescriptions Criteria, MAI: Medication appropriateness index

KDIGO guidelines contain a strong recommendation about statin use in all patients with CKD above the age of 50.[30] High levels of low-density lipoprotein (LDL) cholesterol are a risk factor for cardiovascular disease among adults with CKD.[31,32] The key therapy to lower LDL cholesterol levels includes statins.[31] The risk of atherosclerotic events and mortality can be lowered as much as 25% with statin therapy in adults with CKD.[32] More than half of our patients were prescribed statins (58%) at discharge. This might has been because not all nephrologists in the ward were likely to use KDIGO guidelines or because the guidelines and recommendations differed or due to lack of data from large randomized controlled trials on the side effects of statins in older adults with CKD.[32] These patients are also vulnerable to statin-related myopathy.[24] There are still mixed findings regarding the benefits of statins for adults 75 years or older or frail patients with many comorbidities such as CKD.[24]

Metformin is the first-line treatment in diabetes guidelines.[33] Due to its low cost, low hypoglycemia risk, and potential cardiovascular benefits, metformin is prioritized over other antidiabetic drugs.[33] Initial guidelines suggested not to using metformin if a patient's estimated GFR (eGFR) is less than 60 mL/minute/1.73 m^2.[33] However, recent KDIGO guidelines published in 2020 recommend the use of metformin if the patient's eGFR is more than 30 mL/minute/1.73 m^2.[30] Over the years, the risk of lactic acidosis has diminished with evidence that metformin did not pose a high risk in patients.[33] Therefore, more relaxed rules are now followed for the metformin use based on eGFR. In our study population, a few patients were prescribed metformin, whereas the majority used linagliptin. The possible reasons for preference for dipeptidyl peptidase-4 inhibitors are their availability for use in all stages of CKD, once-daily dosing, low risk of hypoglycemia in patients with CKD and potential cardiovascular and renal benefits.[24]

Beers and STOPP criteria include suggestions for renal dose adjustment, while MAI criteria only include a suggestion for the appropriate dose and are not specific to the renal dose. However, suggestions based on the renal dose are only for a limited number of medications. Beers and STOPP criteria are known as explicit measures that are for universal use in all patients,[20] so they may not cover all case scenarios with medications. MAI is an implicit measure that is more patient-specific but requires a detailed search for patient data and databases.[20] Therefore, although it was time consuming, a detailed search to identify each medication's renal dose was employed in this study using other medication databases. This highlights the need for specific guidelines for older adults with CKD to improve practice.

Most patients had at least one DDI in their discharge prescription (93%). Nearly half of the them had DDIs in either category X or D that required avoiding the combination or modifying the regimen (46%). Most DDIs were in the moderate severity category and required monitoring drug therapy (78.9%). Although a lower number of DDIs was determined according to Beers compared to MAI (13 *vs*. 752), the recommendations from Beers were from clinical observations and thus more likely to be associated with clinically relevant adverse events among older adults.[34] A high number of DDIs were identified by the MAI because the drug interaction checker database was used for the evaluation. Similarly, DDIs were found to be common among older adults with CKD at discharge in Australia.[20] CKD was independently associated with DDIs in older adults.[34] This high number of older adults affected by PIMU showed that there is a need for guidance regarding the appropriate concomitant use of medications by older adults with CKD. Pharmacists have enough skill and knowledge to determine DDIs and make suggestions regarding optimal medication use for this vulnerable group of patients. Our nephrology ward could have benefited from the presence of a clinical pharmacist, who routinely checks for DDIs during discharge and seeks to prevent PIMU. Moreover, educational interventions specific to DDIs are needed to improve existing practices.

In this study, Beers criterion had higher sensitivity (0.97 *vs*. 0.56) and detected more PIMU (11.3% *vs*. 6.4%) than STOPP criteria. The measures of agreement were moderate between 2 sets of criteria. In contrast to our study, a local study conducted among older adults in Türkiye found STOPP criteria were more successful than Beers version 2012 in detecting PIMU.[35] Compared to Beers version 2015, STOPP criteria had the highest sensitivity and measure of agreement among older adults to detect PIMU in a study from Kuwait.[15] The differences might have arisen because the most updated 2019 version of Beers was likely to detect more PIMU among the older adults with CKD since it had renal dose adjustment recommendations from version 2015. Another reason might be the differences in patient characteristics in the studies. This study included only older adults with CKD. The number of older adults with CKD was higher than that of older adults with any comorbidities. Therefore, Beers version 2019 appears more sensitive and able to detect more PIMU in older adults with CKD.

Study limitations

There were several limitations to the present study. Firstly, the study included only the prescription records of the patients. Data on use of dietary supplements without prescription at the time of discharge could not be collected. However, it is routine practice to write down the names of dietary supplements such as vitamins in prescriptions in nephrology wards. Second, the findings could not be generalized to all older adults with CKD due to the limited number of study participants and the study was conducted in a single ward. Finally, the clinical outcomes of PIMU were unknown as this was a retrospective study.

CONCLUSION

In conclusion, the high prevalence of PIMU is a major concern among older adults with CKD. DDIs are the main contributor to PIMU. To detect PIMU, use of Beers criteria seemed appropriate, although there is a great need for more specific guidance. Well-designed coordination between healthcare professionals and especially involving a clinical pharmacist to review the medication prescribed at discharge can help improve appropriate medication use among older adults with CKD.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee for Human Research of the Ankara University Faculty of Medicine (date: September 12, 2019; no: İ3-70-19).

Informed Consent: Since it was a retrospective study, informed consent were not obtainable.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.P., A.S., Design: A.P., A.S., Ş.E., Data Collection or Processing: A.P., A.S., Ş.E., Analysis or Interpretation: A.P., A.S., Ş.E., Literature Search: A.P., A.S., Writing: A.P., A.S., Ş.E., Ş.Er., A.T.Ö.

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