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Potentially inappropriate medication use in elderly patients treated in intensive care units: A cross-sectional study using 2019 Beers, STOPP/v2 Criteria and EU(7)-PIM List

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Abstract

Objective: To determine the prevalence of and the risk factors for Potentially Inappropriate Medication (PIM), the drug groups most commonly evaluated as PIMs in elderly patients in the ICUs by using 2019 Beers Criteria, STOPP version 2 (v2) Criteria and EU(7)-PIM List. The relation between mortality rate and length of ICU stay with PIMs was also examined.

Methods: This was a cross sectional study conducted on patients aged ≥65 years, treated in ICUs (n = 139) between June 8, 2020, and January 11, 2021. Patients' demographic characteristics, clinical data and laboratory findings about the drugs used were collected prospectively. PIMs were evaluated according to each of the criteria applied. Relationship of dependent and independent variables was evaluated using chi-square analysis, *t*-test and logistic regression analysis. $P < .05$ was considered statistically significant.

Results: The number of patients with at least 1 PIM according to three criteria was 118 (84.9%) (80.6%, 59.7%, 48.2%, Beers, STOPP/v2 and EU(7)-PIM List, respectively). In the univariate analysis, receiving renal replacement therapy and high number of drugs were the covariates that significantly affected the presence of PIM according to all three criteria ($P < .05$). Combined use of anxiolytics and opioids in Beers Criteria (58.3%), antipsychotics (26.6%) in STOPP/v2 Criteria, and antiarrhythmics (23.7%) in EU(7)-PIM List were the drugs that caused PIM at most. No relationship was found between the presence of PIM and mortality. The length of ICU stay was determined significantly longer in the presence of PIM according to Beers Criteria ($P = .028$).

Conclusions: In this study, the prevalence of PIM was determined higher in elderly patients in ICU. Our results supported that 2019 Beers Criteria for ICU patients seems to be more directive in detecting PIMs and determining the prognosis. Reducing the number of drugs administered may be the first step to decrease PIMs in elderly patients in ICU and to maintain the treatment safely.

Ferhan Demirer Aydemir and Seyma Oncu contributed equally to this work.

1 | INTRODUCTION

Potentially Inappropriate Medications (PIMs) are the drugs with higher risks in elderly than their expected benefits and rather be avoided if can be replaced by safer alternatives.[1,2] They can increase morbidity and mortality.[3-5]

First, the American Geriatrics Society Beers Criteria (1991) was developed for evaluating the use of PIM in the treatment of elderly, updated many times until 2019, and widely used in scientific and clinical practices.[6,7] The Screening Tool of Older Persons' Prescriptions (STOPP) Criteria classifying drugs according to physiological systems and based on drugs available in Europe, was first established in 2008, then updated in 2015 (STOPP/v2), and widely used as the Beers Criteria.[2,8,9] Laboratory and clinical data of patient are needed while evaluating PIM according to these Beers and STOPP/v2 criteria. The 2015 EU(7)-PIM List is another tool commonly used in European countries, requiring less clinical information than other two criteria.[10] These criteria were developed mainly for the safe and effective treatment of elderly outpatients, although they are mostly applied to hospitalized patients.

Patients at ≥65 years constitute approximately 50% of intensive care unit (ICU) patients.[11] Their treatments are special and different due to acute development and critical urgency of their diseases.[12] There is limited information about the use of existing criteria to evaluate the appropriateness of medications used in the treatment of elderly ICU patients. It is recommended to use the updated 2019 Beers Criteria in all patients aged ≥65, except for palliative care.[7] To the best of our knowledge, there is no prospective study in the literature evaluating the appropriateness of the drugs used throughout ICU stay of elderly, with these criteria.[13,14] Treatment protocols of elderly can vary widely due to the dynamic nature of critical illnesses during ICU stay. Besides, several physicians' involvement in patients' treatments, inadequate coordination between physicians and insufficient time allocated for consultation may cause increased use of PIMs.[15] Therefore, evaluating the use of PIMs during ICU stay is important.

In a study comparing the effectiveness of Beers 2012 and STOPP/v2 Criteria in determining the prevalence of PIM in patients admitted to the geriatric outpatient clinic in Turkey, the prevalence was found to be 33.3% and 39.1%, respectively.[16] In another study that performed the evaluation according to the STOPP/v1 criteria, the prevalence was approximately 41%.[17] In two other studies performed with geriatric cancer patients, the prevalence of PIM was reported to be approximately 30% according to the Beers 2012 Criteria and 16% according to the STOPP/v1 Criteria.[18,19] The studies conducted in Turkey and reported in the literature are limited number and they do not include ICU patients. Actually, the number of studies conducted with ICU patients are limited in other countries as well. In these studies, the prevalence of PIM was reported to be between 20–80% according to the 2012 and 2015 Beers Criteria, around 45% according to the STOPP/v2 Criteria, and around 50% according to the EU(7)-PIM List.[20-24] Considering all these issues, there is an apparent need for prospectively designed studies with elderly ICU patients in order to determine and compare the prevalence of PIM using the current Beers (2019) Criteria, STOPP/v2 Criteria and the EU(7)-PIM List. Therefore, in this study, we aimed to evaluate (a) the prevalence of PIM, (b) risk factors affecting the prevalence of PIM and (c) medication groups most frequently evaluated as PIMs, by using 2019 Beers Criteria, STOPP/v2 Criteria and 2015 EU(7)-PIM List in elderly patients during their stay in the ICUs. Additionally, relationship between patients' 28-day mortality rates and length of stay in the ICU with PIM were also examined. There was no accepted screening tool in Turkey when the study was planned. For this reason, an evaluation was also made with the STOPP/v2 Criteria and the EU(7)-PIM List developed in Europe with a view to better represent the drugs and patient population in Turkey, and for intercountry comparison and transferability of the results to Turkey. Because the drugs covered by the Beers Criteria developed in the USA may differ from the drugs in Europe.[25] Later on, Turkish Inappropriate Medication Use in the Elderly (TIME) criteria was published.[9,26] It would be appropriate to use the TIME Criteria as well.

What's known

- Elderly patients treated in intensive care units (ICUs) have increased prevalence of multimorbidity, physiologic and psychological changes, and are likely to require multiple medications to manage. As a result, they may be at increased risk for potentially inappropriate medication (PIM) use. Avoiding PIM to reduce drug-related mortality and morbidity is an important strategy.
- However, few studies have evaluated the prevalence of PIM and highlighted screening tools available for PIM identification in elderly patients treated in ICU.

What's new

- PIM use was found to be high in elderly ICU patients. Of the three screening tools, the prevalence of PIM determined by the 2019 Beers Criteria was higher than that of STOPP/v2 and EU(7)-PIM List. Antipsychotics and amiodarone were among the common PIMs for all three criteria. Risk factors associated with PIM showed variances according to all three criteria. However, the prevalences of PIM determined according to all three criteria were positively associated with the number of drugs used in the treatments, although it was not significant according to the STOPP/v2 criteria. The length of ICU stay was significantly longer for the patients with higher PIM according to the 2019 Beers Criteria.

2 | METHODS

2.1 | Setting and sample

This is a cross sectional, prospective study, conducted with patients aged ≥65 hospitalized for reasons other than COVID-19 in Dokuz Eylül University Research and Application Hospital Internal Diseases ICU and Anesthesia ICU between June 8, 2020, and January 11, 2021.

Based on the literature, the sample size was calculated to be at least 139 patients by the Open Epi program, the PIM prevalence was accepted as 77%, with a precision of 7% and a confidence level of 95%.[13] The study continued until the target number of patients was reached.

Inclusion criteria: Elderly patients aged ≥65, who could give informed consent directly or via their relatives. Exclusion criteria: Patients not taking any medication, staying in the ICU for <48 hours, having <6 months life expectancy, and being diagnosed with severe and terminal disease.

During data collection period, 204 patients were admitted to the ICUs, 65 patients were excluded from the study (31 patients stayed in the ICUs for <48 hours; 15 had life expectancy <6 months; consent was not obtained from 19 patients) (Figure 1).

The research started after the approval of the Non-Interventional Research Ethics Committee of Dokuz Eylül University (2020/11-35) and was conducted in accordance with the principles of the Declaration of Helsinki.

2.2 | Study variables and data collection

PIM was the dependent variable of the study while the independent variables were age (year), gender (female/male), body mass index (BMI, kg/m^2), number of comorbidities, mechanical ventilation (MV) and/or renal replacement therapy (RRT) and the number of medications. In addition, Charlson Comorbidity Index (CCI), Glasgow Coma Scale (GCS) and Acute Physiology and Chronic Health Evaluation (APACHE) II Score, determining the prognosis in intensive care patients, were recorded. CCI predicts one-year mortality with respect to comorbidity status, GCS evaluates the state of consciousness by scoring responses to eye/verbal/motor stimuli, and APACHE II Score evaluates the disease severity in ICU patients. The risk of mortality increases with high CCI, low GCS and high APACHE II scores.[27-31] Additionally, the effect of PIM on 28-day mortality and length of ICU stay was examined prospectively, according to three criteria. A "case form" was arranged for each patient. Demographic characteristics (age, gender, height, weight, body mass index, diagnosis at admission, comorbidity, referral), mortality data (time and cause of death) and length of ICU stay were recorded in these forms. Information about drug use (active substance, dose and number of intake), laboratory findings (serum creatinine, BUN, GFR, sodium, potassium), MV and/or RRT were recorded daily during the entire ICU stay. Each hospitalization of a patient was taken as a different patient. Deaths occurred in the first 28 days after admission to the ICU were recorded for mortality. Mortality data of patients discharged from the ICU earlier than 28 days were obtained from electronic records.

2.3 | Evaluation of PIMs

PIMs were evaluated using 2019 Beers Criteria, STOPP/v2 Criteria and EU(7)-PIM List of the drugs used by the patients in ICU.[7,8,10] Analysis was performed according to four Beers Criteria (*1-Potentially inappropriate medication use in older adults; 2-Potentially inappropriate medication use in older adults due to drug-disease or drug-syndrome interactions that may exacerbate the disease or syndrome;*

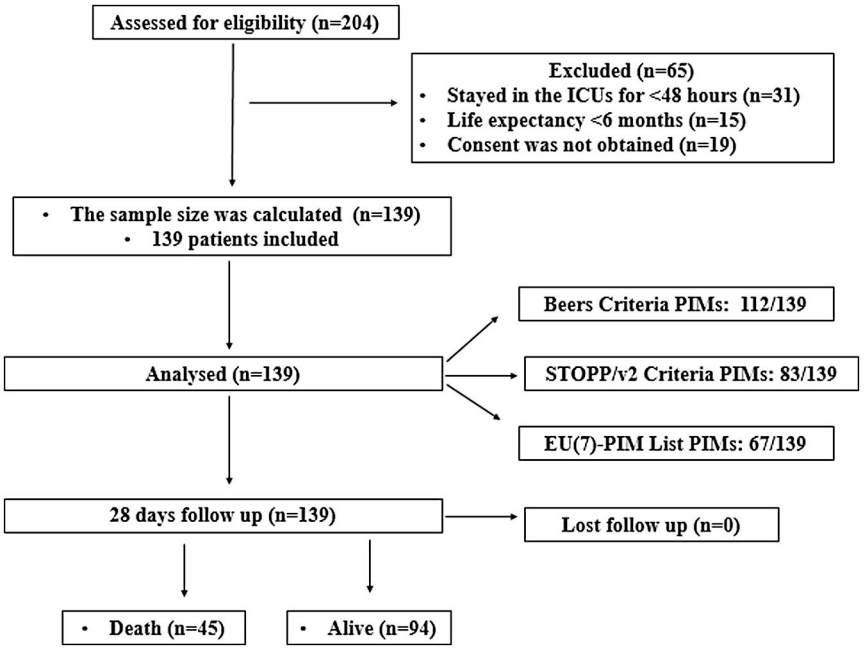

FIGURE 1 Flow chart of study population

3- Potentially clinically important drug-drug interactions that should be avoided in older adults; 4- Medications that should be avoided or have their dosage reduced with varying levels of kidney function in older adults). Two STOPP Criteria (category A1: Any drug prescribed without evidence-based clinical indication. A2: Any drug prescribed beyond the recommended duration, where treatment duration is well defined) were not included in statistical analysis. An evaluation was made according to the entire EU(7)-PIM List. Proton pump inhibitors usage for over 8 weeks, that is accepted as PIM according to all three criteria, was not included in the analysis because the duration of stay in the ICU was less than 8 weeks. Scoring for PIMs for each patient was performed manually by a trainee pharmacologist and checked by an advisor.

2.4 | Statistical analysis

Descriptive statistics was implemented for the demographic data of each hospitalization and the presence of PIM. Results were given as number (n), percentage (%), mean, standard deviation (SD) and median (interquartile range). Chi-square analysis was used to assess the relation between dependent and independent variables. The independent variables, namely BMI, MV and/or RRT, CCI, GCS, APACHE II Score and the number of drugs used, were divided into two groups according to median values to be analysed. Multivariate analysis (logistic regression analysis) was performed between the presence of PIM and independent variables. Independent variables with P values <.25 in the univariate analysis were included in the multivariate model.[32,33] The relationship between PIMs and 28-day mortality was assessed by Chi-square analysis, while between PIM and the average number of days at ICU by the students' t-test (data were tested for normality with the Shapiro-Wilk test). Kaplan Meier survival analysis was performed for 28-day mortality according to the presence of PIM with all three criteria and Log-Rank test was used. The consistency between the three criteria used in determining the presence of PIM was evaluated by the Kappa test (values of kappa >0.75 indicated good to excellent agreement; 0.40-0.75 moderate agreement; <0.40 poor agreement).[33] Data were analysed by SPSS-24 (SPSS Inc., Chicago, IL, USA) statistical program and $P < .05$ was considered statistically significant.

3 | RESULTS

Mean age of 139 patients was 76.7 (7.7) with a range of 65-102 years, with 51.1% (n = 71) were male. Respiratory system diseases were the most common diagnosis at admission (38.1%). Mean number of drugs administered during hospitalization was 10.1 (3.2) with a range of 3-20 days. MV was implemented in 89.2% (n = 124) of the patients during hospitalization, while RRT in 18.7% (n = 26). Mean length of stay in ICUs was 12.2 (9.9) days. Mortality occurred in 32.4% of the patients during ICU stay (Table 1).

TABLE 1 Characteristics of the study sample (n = 139)

Characteristics	n (%)
Age (year)	
65-74	65 (46.8)
75-84	50 (36.0)
85 and over	24 (17.3)
Gender	
Male	71 (51.1)
Female	68 (48.9)
Place of residence	
House	134 (96.4)
Nursing home/residential home	5 (3.6)
Diagnosis at admission	
Respiratory diseases	53 (38.1)
Infection	32 (23.0)
Cerebrovascular diseases	23 (16.6)
Gastrointestinal system diseases	21 (15.1)
Other	10 (7.2)
Discharge status	
Admission to internal medicine service	49 (35.3)
Admission to surgery service	37 (26.6)
Mortality	45 (32.4)
Discharged home	8 (5.8)
	Median (Q1-Q3)
Disease severity scores	
Charlson Comorbidity Index Score	6 (5-9)
Glasgow Coma Scale Score	9 (5-14)
APACHE II Score	22 (16-30)
Body mass index (kg/m^2)	25 (23-28)
Number of comorbidities	3 (2-5)

Note: Q1-Q3: Interquartile range.

3.1 | Presence of PIM and affecting factors

The number of patients with at least one PIM as identified by three criteria was 118 (84.9%). At least one PIM was determined in 80.6% (n = 112) of the patients according to the Beers Criteria, in 59.7% (n = 83) according to the STOPP/v2 Criteria, and 48.2% (n = 67) according to the EU(7)-PIM List. The number of PIMs was between 0 (27 patients, 19.4%) and 5 (2 patients, 1.4%) according to Beers Criteria, 0 (56 patients, 40.3%) and 4 (3 patients, 2.2%) according to the STOPP/v2 Criteria, and 0 (72 patients, 51.8%) and 2 (20 patients, 14.4%) according to the EU(7)-PIM List.

The factors statistically significantly affecting the presence of PIM according to Beers Criteria were RRT, high CCI, low GCS, high APACHE II Score and high number of drugs. The presence of PIM was not found to be significantly related with increasing age and MV support. The factors affecting the presence of PIM statistically significantly according to the EU(7)-PIM List were RRT, low GCS, high

TABLE 2 Factors affecting PIM according to the 2019 Beers Criteria, STOPP/v2 Criteria and EU(7)-PIM List

	2019 Beers Criteria PIM presence (n = 112) n(%)	*P*[a] value	STOPP/v2 Criteria PIM presence (n = 83) n(%)	*P*[a] value	EU(7)-PIM List PIM presence (n = 67) n(%)	*P*[a] value
Age (years) (n)						
65-74 (65)	49 (75.4)	.328	37 (56.9)	.471	30 (46.2)	.903
75-84 (50)	42 (84.0)		29 (58.0)		25 (50.0)	
≥85 (24)	21 (87)		17 (70.8)		12 (50.0)	
Gender (n)						
Female (68)	56 (82.4)	.604	41 (60.3)	.891	35 (51.5)	.450
Male (71)	56 (78.9)		42 (59.2)		32 (45.1)	
Body mass index (n)						
<25 (62)	50 (80.6)	.985	36 (58.1)	.722	28 (45.2)	.520
≥25 (77)	62 (80.5)		47 (61.0)		39 (50.6)	
Mechanic ventilation (n)						
Yes (124)	101 (81.5)	.453	73 (58.9)	.561	60 (48.4)	.900
No (15)	11 (73.3)		10 (66.7)		7 (46.7)	
Renal replacement therapy (n)						
Yes (26)	26 (100.0)	*.005*	21 (80.8)	*.015*	19 (73.1)	*.005*
No (113)	86 (76.1)		62 (54.9)		48 (42.5)	
Charlson Comorbidity Index (n)						
≤6 (65)	44 (67.7)	*<.001*	34 (52.3)	.095	26 (40.6)	.083
>6 (74)	68 (91.9)		49 (66.2)		41 (55.4)	
Glasgow Coma Scale (n)						
≤9 (70)	62 (88.6)	*.016*	38 (54.3)	.189	41 (58.6)	*.014*
>9 (69)	50 (72.5)		45 (65.2)		26 (37.7)	
APACHE II (n)						
≤22 (70)	47 (67.1)	*<.001*	38 (54.3)	.189	24 (34.3)	*.001*
>22 (69)	65 (94.2)		45 (65.2)		43 (62.3)	
Number of drugs (n)						
≤10 (70)	48 (68.6)	*<.001*	36 (51.4)	*<.045*	24 (34.3)	*.001*
>10 (69)	64 (92.8)		47 (68.1)		43 (62.3)	

[a]*P* values are obtained from chi-square analysis.

APACHE II Score and high number of drugs, similar to the Beers Criteria. The presence of PIM increased with increasing values of CCI, which was not statistically significant. The factors significantly affecting the presence of PIM according to the STOPP/v2 Criteria were RRT and high number of drugs (Table 2). The common variables significantly affecting the presence of PIM according to three criteria were RRT and high number of drugs.

According to multivariate analysis results; high CCI, APACHE II Score and number of drugs according to the Beers Criteria; RRT and low GCS according to the STOPP/v2 Criteria; high number of drugs according to the EU(7)-PIM List remained significant in the model (Table 3).

Kappa value was 0.363 for Beers Criteria and STOPP/v2 Criteria; 0.310 for Beers Criteria and EU(7)-PIM List; and 0.400 for STOPP/v2 and EU(7)-PIM List. Assessing the presence of PIM, concordance between STOPP/v2 and the EU(7)-PIM List was moderate while between the Beers Criteria and the other two criteria was weak.

3.2 | Drugs most commonly evaluated as PIM

Combined use of anxiolytics and opioids was the most common PIM in 58.3% (n = 81) of the patients, according to the Beers Criteria. Antithrombotics used in 29.5% (n = 41), propulsives in 25.2% (n = 35) and antipsychotics used in 24.5% (n = 34) patients were following that. According to the STOPP/v2 Criteria, antipsychotics in 26.6% (n = 37), antithrombotics in 20.9% (n = 29) and antiarrhythmics in 18.0% (n = 25) of the patients caused PIM primarily. According to the EU(7)-PIM List, PIM occurred mostly due to antiarrhythmics in

TABLE 3 Multivariate analysis of the factors affecting the presence of PIM according to the 2019 Beers Criteria, STOPP/v2 Criteria and EU(7)-PIM List

	2019 Beers Criteria[a]		STOPP/v2 Criteria[b]		EU(7)-PIM List	
Variables	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Renal replacement therapy	n/d	.998	3.087 (1.010-9.434)	*.048*	2.689 (0.971-7.449)	.057
Charlson Comorbidity Index	5.011 (1.599-15.708)	*.006*	1.327 (0.632-2.786)	.455	1.301 (0.610-2.778)	.496
Glasgow Coma Score	1.710 (0.544-5.368)	.358	2.424 (1.072-5.479)	*.033*	1.558 (0.716-3.390)	.264
APACHE II Score	6.130 (1.716-21.905)	*.005*	1.606 (0.721-3.579)	.246	2.049 (0.940-4.471)	.071
Number of medications	4.254 (1.289-14.040)	*.017*	1.945 (0.962-3.931)	.064	2.542 (1.199-5.390)	*.015*

Notes: Reference categories: no renal replacement therapy; Glasgow Coma Score > 9; Charlson Comorbidity Index < 6; APACHE II Score < 22; Number of medications < 10. n/d: OR (CI%95) could not be defined due to zero value in one cell.

[a]Potentially inappropriate medications (PIMs) with considering inappropriate medication; drug–disease or drug–syndrome interactions; drug-drug interactions; dosage reduced with levels of kidney function.

[b]Potentially inappropriate medications (PIMs) without considering evidence-based clinical indication; prescribed beyond the recommended duration.

23.7% (n = 33), propulsives in 19.4% (n = 27), and antipsychotics in 10.8% (n = 15) of the patients (Table 4).

3.3 | 28-day mortality and length of ICU stay with respect to the presence of PIM

According to three criteria, the 28-day mortality rate was higher in the presence of PIM, but it was not significant. Only according to the Beers Criteria, the length ICU stay was determined significantly longer in the presence of PIM (Table 5). Median survival time was 28 days for those with PIM according to three criteria. There was no significant difference in terms of survival between patients with and without PIM according to three criteria.

4 | DISCUSSION

This study is the first study comparing the prevalence of PIM in elderly patients hospitalized in the ICUs according to 2019 Beers, STOPP/v2 Criteria and EU(7)-PIM List, where PIM prevalence was found as 80.6%, 59.7% and 48.2%, respectively. PIM determined by Beers Criteria almost covered the PIMs determined by other two criteria. The use of antipsychotics and antiarrhythmics was among the most frequently detected PIMs for three criteria. Increased number of drugs significantly affected the presence of PIM according to both Beers Criteria and the EU(7)-PIM List, although PIM risk factors varied for all three criteria in multivariate analysis. The presence of PIM as described by the Beers Criteria, was found to be associated with a longer ICU stay.

Our results are compatible with the retrospective study by Rahman et al, reporting the presence of at least one PIM according to the 2015 Beers and STOPP Criteria, in 77% and 43% of the patients discharged from ICU, respectively.[13] Similarly, at least one PIM use was noted in 98.2% of the ICU patients aged ≥60 according to 2012 Beers Criteria in a retrospective Brazilian study, and in more than 80% of the patients at ICU admission in another study by Floroff et al.[20,21] PIM prevalence was 49.8% and 21.8%, respectively, according to the EU(7)-PIM List and 2015 Beers Criteria in a retrospective study conducted in India with elderly in the ICU and internal medicine service,[22] where the prevalence as determined by the Beers Criteria was considerably lower than our results while EU(7)-PIM List results were similar. At least one PIM, as identified by the 2015 Beers Criteria, was noted in approximately 33% of elderly patients hospitalized in the ICU of the university hospital in Jordan,[23] which was also considerably lower with respect to our results. Again, in another study conducted retrospectively in the ICU of a 3rd level hospital in China, one or more PIM was reported in 58.1% and 44.0% of the patients according to the 2015 Beers and STOPP/v2 Criteria, respectively.[24] The variances in the results of the studies using the Beers Criteria may be related to the specific items defined within Beers Criteria, which is compiled under 5 titles. PIM was evaluated according to the drugs listed under the title of "*potentially inappropriate medication use in older adults*", especially in studies reporting lower rates. Besides that, the version of the Beers Criteria used, the study design, the drugs available in the study centres, and patient population variations may also have caused variations in results.

In accordance with the literature, in this study too, a positive relationship between the number of drugs used and the presence of PIM displayed significance in univariate analysis for three criteria,[2,20,34] whereas lost its significance for the STOPP/v2 Criteria in multivariate analysis. The presence of PIM was also influenced by worsened clinic related scores besides the number of drugs. Similarly, the number of PIMs was found to be significantly higher according to the Beers Criteria and STOPP Criteria in neurologically damaged and critically ill elderly patients with low GCS and high APACHE II scores.[21] In our study, RRT also affected the presence of PIM according to all 3 criteria in univariate analyses. Although there are no studies evaluating RRT and the presence of PIM in the literature, increased number of PIM was reported in the presence of chronic renal failure or due to decreased GFR rate, according to all three criteria.[35,36]

Antipsychotics and benzodiazepines were defined as PIMs according to three criteria. However, both drug groups are widely used

TABLE 4 Most common drugs identified as PIM in ICU according to the 2019 Beers Criteria, STOPP/v2 Criteria and EU(7)-PIM List

	Drug class (ATC code) most common medication within drug class	Overall use	Criteria for inappropriate use
Potentially Inappropriate Medication identified by 2019 Beers Criteria	Nervous system (N)		
	Anxiolytics and opioids (N05B/N02A) • Fentanyl and Midazolam	58.3% (n = 81)	Drug-drug interactions
	Antipsychotics (N05A) • Quetiapine	13.7% (n = 19)	Avoid antipsychotics for behavioural problems of dementia or delirium unless nonpharmacological options have failed or are not possible and the older adult is threatening substantial harm to self or others
	• Haloperidol	10.8% (n = 15)	
	Antiepileptics (N03A) • Levetiracetam	7.9% (n = 11)	Drug-drug interactions
	Anxiolytics (N05B) • Diazepam	2.8% (n = 4)	All benzodiazepines increase risk of cognitive impairment, delirium, falls, fractures in older adults
	• Alprazolam	0.7% (n = 1)	
	Antidepressants (N06A) • Escitalopram	2.9% (n = 4)	Drug-drug interactions
	Opioids (N02A) • Tramadol	2.8% (n = 4)	Potentially inappropriate medications based on kidney function
	Blood and blood forming organs (B)		
	Antithrombotic Agents (B01A) • Enoxaparin	29.5% (n = 41)	Potentially inappropriate medications based on kidney function
	Alimentary Tract and Metabolism (A)		
	Propulsives (A03F) • Metoclopramide	25.2% (n = 35)	Can cause extrapyramidal effects, including tardive dyskinesia; risk may be greater in frail older adults and with prolonged exposure
	Drugs for Peptic Ulcer and GOR Disease (A02B) • Ranitidine	7.2% (n = 10)	Potentially inappropriate medications based on kidney function
	Cardiovascular system (C)		
	Antiarrhythmics, Class I and III (C01B) • Amiodarone	15.8% (n = 22)	Avoid as first-line therapy for atrial fibrillation unless patient has heart failure or substantial left ventricular hypertrophy
	Cardiac Glycosides (C01A) • Digoxin	2.8% (n = 4)	Avoid this rate control agent as first line therapy for atrial fibrillation
Potentially Inappropriate Medication identified by STOPP/v2 Criteria	Nervous system (N)		
	Antipsychotics (N05A) • Quetiapine	15.8% (n = 22)	Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia
	• Haloperidol	10.8% (n = 15)	
	Opioids (N02A) • Tramadol	7.9% (n = 11)	Use of oral or transdermal strong opioids as first line therapy for mild pain
	• Morfin	7.2% (n = 10)	
	Antidepressants (N06A) • Escitalopram	0.7% (n = 1)	Selective serotonin reuptake Inhibitor (SSRIs) with current or recent significant hyponatraemia
	Blood and blood forming organs (B)		
	Antithrombotic Agents (B01A) • Enoxaparin	20.9% (n = 29)	Factor Xa inhibitors if eGFR < 15 (risk of bleeding) Any duplicate drug class prescription Factor Xa inhibitors with concurrent significant bleeding risk
	Cardiovascular system (C)		
	Antiarrhythmics, Class I and III (C01B) • Amiodarone	18.0% (n = 25)	Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias
	Cardiac Glycosides (C01A) • Digoxin	1.4% (n = 2)	Digoxin for heart failure with preserved systolic ventricular function

(Continues)

TABLE 4 Continued

	Drug class (ATC code) most common medication within drug class	Overall use	Criteria for inappropriate use
Potentially Inappropriate Medication identified by EU(7)-PIM List	Cardiovascular system (C)		
	Antiarrhythmics, Class I and III (C01B) • Amiodarone	23.7% (n = 33)	Associated with QT interval problems and risk of provoking torsades de pointes Above the recommended dose
	Cardiac Glycosides (C01A) • Digoxin	2.8% (n = 4)	Elevated glycoside sensitivity in older people; risk of intoxication Above the recommended dose
	Alimentary tract and metabolism (A)		
	Propulsives (A03F) • Metoclopramide	19.4% (n = 27)	Antidopaminergic and anticholinergic effects, may worsen peripheral arterial blood flow and precipitate intermittent claudication, Above the recommended dose
	Drugs for Peptic Ulcer and GOR Disease (A02B) • Ranitidine	7.2% (n = 10)	CNS adverse effects including confusion Above the recommended dose
	Nervous system (N)		
	Antipsychotics (N05A) • Haloperidol	10.8% (n = 15)	Anticholinergic and extrapyramidal side effects Above the recommended dose
	Opioids (N02A) • Tramadol	4.3% (n = 6)	More adverse effects in older people Above the recommended dose

Note: ATC codes are Anatomical Therapeutic Classification codes.

TABLE 5 The relationship of the presence of PIM with 28-day mortality and length of ICU stay according to the 2019 Beers Criteria, STOPP/v2 Criteria and EU(7)-PIM List

		Mortality n (%)	*P*[a] value	Length of stay in intensive care unit (day), mean (SD)	*P*[b] value
2019 Beers Criteria	Potentially inappropriate medication (n = 112)	46 (41.1)	.069	13.1 (10.4)	*.028*
	No potentially inappropriate medication (n = 27)	6 (22.2)		8.4 (6.6)	
STOPP/v2 Criteria	Potentially inappropriate medication (n = 83)	33 (39.8)	.486	11.8 (9.5)	.660
	No potentially inappropriate medication (n = 56)	19 (33.9)		12.6 (10.6)	
EU(7)-PIM List	Potentially inappropriate medication (n = 67)	28 (41.8)	.303	13.1 (11.1)	.295
	No potentially inappropriate medication (n = 72)	24 (33.3)		11.3 (8.8)	

[a]*P* values are obtained from chi-square analysis.

[b]*P* values are obtained from *t*-test.

in ICUs.[20] Antipsychotics were reported to be used in approximately 20%-36% of ICU patients aged ≥65.[37,38] In our study too, antipsychotics (quetiapine and haloperidol), used in delirium treatment in the ICUs, were among the most common drug groups causing PIM, according to three criteria. Delirium is an acute cerebral dysfunction occurring in more than half of the elderly patients in ICUs with limited treatment options.[39,40] For this reason, prevention of delirium and elimination of risk factors were preferred rather than its treatment. The role of antipsychotics in its treatment is controversial.[41,42]

As for drug-drug interaction within Beers Criteria, the most common PIM in our study was the combined use of opioids and benzodiazepines, which was preferred in patients receiving MV support. It was pointed out as a combination to be avoided, due to increased risk of toxicity.[7] Furthermore it was also noted that all benzodiazepines could increase the risk of cognitive impairment and delirium.[7] Jung SY et al indicated that 62% of the sedative agents used in elderly patients with MV were midazolam, 51% of the analgesics were opioid analgesics, antipsychotic use was higher in patients using benzodiazepines than those using non-benzodiazepines; and delirium was more common among the patients using benzodiazepines.[38] Similarly, Zaal IJ et al informed that benzodiazepines may be associated with delirium in critically ill patients, and benzodiazepines

at doses equivalent to 5 mg of midazolam would increase the risk of delirium by 4%.[43] Benzodiazepines are recommended for sedation while opioids for analgesia in intensive care patients, especially in those with anxiety and agitation.[44] Considering the risk of delirium due to benzodiazepines, however, the use of sedative agents like propofol or dexmedetomidine, less correlated with delirium, may be more beneficial in elderly patients.[45]

Antithrombotic drugs (enoxaparin) were the second drug group that caused the highest PIM, according to both Beers and STOPP/v2 Criteria. In the study by Chahine et al, PIM was evaluated with the 2019 Beers Criteria in patients diagnosed with chronic renal failure, and enoxaparin was accepted as PIM at a rate of 25%, similar to the rate in our study.[46] In another study, antithrombotic drugs used in elderly patients who were hospitalized and had severe bleeding risk, were accepted as PIM according to STOPP/v2 Criteria at a rate of 19.4%.[47] Enoxaparin is recommended for antithrombotic therapy in haemodialysis patients.[48] However, its dose was not adjusted according to GFR in our study, and this was recognized as PIM by both STOPP/v2 and 2019 Beers Criteria, causing the frequency of PIM in patients receiving RRT to significantly increase. Therefore, conscientious dosing will reduce the PIM rate.

Metoclopramide is a drug to be avoided according to Beers Criteria while dose adjustment is recommended in the EU(7)-PIM List. Galli et al determined the rate of PIM related to metoclopramide as 28.6% for patients in ICUs aged 60 and over according to 2012 Beers Criteria, which was consistent with our result.[20] Metoclopramide is commonly used in ICU patients to increase gastrointestinal motility and to support enteral nutrition.[49] However, it should be kept in mind that extrapyramidal side effects, particularly tardive dyskinesia, may develop in elderly individuals.

Amiodarone was one of the most common drugs causing PIM according to all 3 criteria (15.8%-23.7%). Amiodarone was identified as PIM at a rate of 10.9%-37.7% by previous versions of the Beers Criteria in various studies conducted with elderly inpatients and outpatients.[50-52] Our results are similar to the results in the literature. However, amiodarone is a commonly used drug in rhythm control, especially in ICU patients with severe and unstable hemodynamics.[53] Thus, Chang et al, did not accept amiodaron as a PIM due to the opinions of cardiologists, and did not evaluate in the study.[54] In such a case, instead of accepting amiodarone as PIM, proper dose adjustment and careful administration can be recommended, as in the EU(7)-PIM List.

In our study, the length of ICU stay was significantly longer in the presence of PIM, as identified by the Beers Criteria. Likewise, Galli et al also found a relation between the number of PIMs according to 2012 Beers Criteria and the length of stay in the ICU.[20] In our study, the 28-day mortality rate was higher in the presence of PIM, according to all 3 criteria, but this was not significant. There was no relation between the presence of PIM and mortality according to the Beers and STOPP Criteria in two studies conducted with elderly patients in ICU.[13,21]

Increased use of the benzodiazepine-opioid combination, accepted as PIM with drug-drug interaction according to Beers Criteria but not evaluated as PIM according to the other two criteria, might be the reason for the poor consistency between Beers Criteria and other two criteria in our study.

The fact that the study was conducted in a single centre and included only the patients hospitalized in internal diseases ICU and anesthesia ICU limits the general validity of the results to all elderly intensive care patients. Nonetheless, Beers Criteria is a screening tool used in the USA whereas STOPP/v2 Criteria and EU(7)-PIM List in Europe. The fact that these three criteria were not designed for use in Turkey is another limitation of the study. The high prevalence of PIM may be due to small sample size[55,56] as well as the factors like frequent change of drugs in the ICUs and using more drugs in the elderly patients hospitalized in the ICUs since these cases are generally more severe, more fragile, and with higher number of comorbidities.

Prospective study design is one of the advantages of the study. Thus, the patient information (diagnosis, clinical status, laboratory results, etc) required for performing PIM evaluation according to Beers Criteria and STOPP/v2 Criteria were not lost.

5 | CONCLUSION

In this study, at least one PIM was identified in nine out of ten ICU patients in the three sets of criteria. PIM prevalence determined according to Beers Criteria was higher than STOPP/v2 Criteria and EU(7)-PIM List. Antipsychotics and amiodarone were among the most frequently identified PIMs for all three criteria. Increased number of drugs was associated with use of more PIMs according to both Beers Criteria and the EU(7)-PIM List, although PIM risk factors varied for all three criteria. Mortality was approximately 2 times higher (but not significant) in patients with PIM according to Beers Criteria, and length ICU stay was significantly longer. Our results support that Beers Criteria may be more guiding than the other two criteria in detecting PIM and determining prognosis. Early identification of PIM is significant for preventing adverse effects and sustaining the treatment of elderly patients more safely. Reducing the number of drugs used in the treatment and modifying the dose of some drugs can be considered as an initial step to lower PIM. However, it should be kept in mind that PIM is a potential inappropriateness, not a definite one. A detailed clinical assessment is always required in addition to a full review of medical records. Close attention should be paid when applying these criteria in ICU, since the benefit/risk assessment may differ in ICU patients.

DISCLOSURES

The authors declare no conflict of interest.

ETHICS APPROVAL

Dokuz Eylul University Ethical Committee for Non-Interventional Research approved this study (2020/11-35).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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