

Older adult females hospitalized with cardiovascular disease outweigh male older adults in receiving Potentially Inappropriate Medication

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Abstract

Introduction: There are a lack of potentially inappropriate medications (PIMs) predictors among the geriatric population with cardiovascular disease (CVD). **Objective:** This study was focussed on finding out the predictors and prevalence of PIMs use in the older adult patients hospitalized with cardiovascular disease. **Methods:** This prospective cross-sectional study included 250 older adult patients (mean age 69.03 ± 5.76 years) with the CVD having age 65 years or more, admitted in the cardiology/medicine department of a tertiary care hospital. PIMs were identified as per Beers criteria 2019. Binary Logistic regression analysis was used to determine the predictors of PIMs use in older adult patients. **Results:** Results indicate a very high PIM prescription rate of more than 62.4% ($n=156$) with Proton pump inhibitor, short acting insulin according to sliding scale, Enoxaparin $<30\text{ml/min}$ as the most commonly prescribed PIMs. On Binary logistic regression, important predictors for PIMs use were found to be females (odds ratio [OR] 2.36, 95% confidence interval (CI) 1.36- 4.09, $P=0.002$), three diagnosis (OR 4.29, 95% CI 1.31- 14.0, $P=0.016$), [?]4 diagnosis (OR 4.8, 95% CI 1.49- 15.44, $P=0.009$), 7-9 days of hospital stay (OR 4.74, 95% CI 1.07- 20.96, $P=0.04$), [?] 9 medications per day (OR 0.09, 95% CI 0.01- 0.50, $P=0.006$). **Conclusion:** The prevalence of PIMs in older adults with cardiovascular disease is very high, and females with CVD have emerged as a potential PIM indicator. The study also indicates a lack of awareness towards Beer criteria in health care workers (physicians/pharmacists/nursing staff) leading to PIM.

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Running title: Inappropriate prescribing in older adult patients

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Methods: This prospective cross-sectional study included 250 older adult patients (mean age 69.03 ± 5.76 years) with the CVD having age 65 years or more, admitted in the cardiology/medicine department of a tertiary care hospital. PIMs were identified as per Beers criteria 2019. Binary Logistic regression analysis was used to determine the predictors of PIMs use in older adult patients.

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Conclusion: The prevalence of PIMs in older adults with cardiovascular disease is very high, and females with CVD have emerged as a potential PIM indicator. The study also indicates a lack of awareness towards Beer criteria in health care workers (physicians/pharmacists/nursing staff) leading to PIM.

Keywords: Beers Criteria, Cardiovascular disease, older adult patient, potentially inappropriate medication

Impact of findings on practice statements

- Increased prescribing of Potentially Inappropriate Medication among older female patients with cardiovascular disease is a serious health issue that warrants immediate medical attention.
- The high prevalence of medications that should be avoided or their dosage reduced according to the kidney function of the older adult patient shows the need of medication management while prescribing in older adults.
- Polypharmacy and hyperpolypharmacy is associated with the use of PIM in the older adults.

Introduction

PIM is defined as those medications whose adverse risk outweighs its health benefits, mainly when safer or alternative treatment is available.^[1] PIMs use in the older adults is increasing day by day due to several underlying reasons, including lack of knowledge about the application of Beer criteria among the physicians and health care workers.^[2] PIMs use is also increasing due to a lack of classified PIM predictors for various diseases. Various studies have reported a high prevalence of PIMs in the USA, China, and the Indian older adults and are estimated to be within the range of 25% - 90% as identified by different validated criteria.^[3- 5] The prevalence of CVDs along with other comorbidities is widespread in the older adults. CVDs such as hypertension, coronary heart disease, congestive heart failure, stroke, etc are the most common cause of death among the older adults.^[6] PIM use is very harmful to the geriatric population, specifically to patients suffering from CVD and other comorbidities and can lead to severe outcomes.^[7] Older adults is considered frail and more vulnerable to adverse drug events or any medication-related problems due to polypharmacy/high level polypharmacy to treat comorbidities.^[8] Moreover, age-related changes in the physiology of the older adults might also alter the pharmacokinetics and pharmacodynamics of drugs.^[9] Despite this, PIMs continue to be prescribed as a first-line treatment in the older adults, and the increased prevalence of PIMs in the older adults is an issue of grave concern.^[10] Identify inappropriate use of medication in the older adults having to age 65 years or more is of supreme importance.

Various tools like Beer criteria have been developed to determine the use of PIMs in the older adults and minimize the drug-related problems associated with PIMs use. Numerous studies have been conducted to find out the prevalence and predictors of PIMs in the older adults. Still, very few studies have been conducted to find out the PIMs use in the older adult patients hospitalized with CVD. Studies have documented the prevalence of PIMs in CVD older adult patients in a different health care setting. In a recent study, 87.4% of patients received at least one PIM in cardiology service.^[11] However, there is a complete lack of data on PIMs predictors in older adult patients hospitalized with CVD. Hence, the present study's main objective was to determine the prevalence and predictors of Potentially Inappropriate Medication in older adult patients hospitalized with cardiovascular disease using Beers criteria 2019.

Materials & Methods

A prospective observational cross-sectional study was conducted in a tertiary care teaching hospital of Punjab in north India after obtaining Institutional Ethics Committee (IEC) clearance in accordance with the Indian Council for Medical Research Bioethics guidelines (ERB/UCER/2018/9/3). Patients having age [?] 65

years with a history of cardiovascular disease admitted to the Cardiology/Medicine department willing to participate included in the study after written informed consent.

Data to find out PIM predictors in relation to age, sex, education qualification, clinical features, number of comorbidities, Laboratory and radiological investigations (Serum creatinine value), and drug-related characteristics (number of medications during hospital stay) were noted. All of the patient treatment charts were reviewed daily, and the PIM were identified according to the American Geriatric Society (AGS) updated Beers criteria 2019 applicable to the general population aged over 65 years regardless of the level of frailty or place of residence. The Creatinine clearance (CrCl) value was calculated based on serum creatinine of the patient-reported at the time of admission with the help of the Cockcroft- Gault equation.^[12]

Statistical analysis was carried out by using Stata 16 (Stata Corp) and Statistical Package for the Social Science (SPSS) free version 24.^[13] Numerical data was expressed as mean and standard deviation or median and interquartile range depended on the data's normality distribution. Frequency and percentage were used to express categorical data. The prevalence of PIMs was calculated based on the patient-level as follows.

Prevalence of PIMs= total number of patients with at least one PIMs use/ the total population of the older adult patients hospitalized with cardiovascular disease.

The risk factors related to PIM prescription, including socio-demographic variables like age, gender, number of medications, length of hospital stay, and creatinine clearance of the older adult patients, were assessed using binary logistic regression. The Odds Ratio (OR) with a confidence interval of 95% (CI) was used for the identification of predictors for prescribing PIMs. P-value <0.05 was considered statistically significant.

Results

A total of 250 older adult patients were admitted to the cardiology/medicine department with the cardiac complaints and met inclusion criteria during the study period. Out of 250 inpatients, 60% (n=150) of the patients were males, the median age of the patient at the time of hospital admission was 65 years (range 65- 86 years). About 64% (n= 160) of the patients belonged to the age group of 65- 70 years, followed by 17.6% (n=44) patients aged between 71- 75 years, whereas only 8.8% (n=22) of the inpatients were above 80 years. A very high proportion of the patients (67.2%, n=168) were found to be illiterate. Approximately 16% (n=40) of the patients were a chronic smoker, and the same proportion of patients were found to be a chronic alcoholic, respectively. Table 1 represents the socio-demographic and clinical characteristics of the older adult patients.

It was observed that on average, each patient had 3 diagnosis, and the number of diagnosis ranged from one to seven. However, 36.8% (n=92) of the patients were having [?]4 diagnosis during their hospital stay. Moreover, patients have been categorized according to their length of hospital stay as prolonged hospital stay may increase the risk of adverse drug reaction. The median length of hospital stay was 6 days (range 3- 20 days). Also, it was found that nearly one-sixth of the older adult patients (64%, n=160) were prescribed with nine or more than nine medications during their hospital stay. Most of the patients were either on polypharmacy (5- 9 medications per day) or high- level polypharmacy (>10 medications per day) during their hospital stay. On the other hand, several comorbidities were documented in patients. The majority of the older adult patients suffered from chronic diseases such as Ischemic vascular disease (208 patients), Dilated cardiomyopathy (46 patients), followed by 56 patients with congestive heart failure. Figure 1 describes the prevalence of the chronic disease in 250 older adult patients.

A significant decline in kidney functions is often observed in the majority of the older adult patients. In our study, the mean creatinine clearance was 45.62ml/min (range 5-156). It has been clarified in Beers criteria that certain given medications either should be avoided or their dosage should be adjusted after having an eye on the kidney function or creatinine clearance of the patient. The mean serum creatinine of the patient was 5.6mg/dl (range 2.4- 18). Creatinine clearance (CrCl) was calculated with the help of Cockcroft- Gault formula, and the mean CrCl was 12.75ml/min (range 4- 36). About 37.6% (n= 94) of the patients were having CrCl less than 30ml/min followed by 33.6% (n=84) within the range between 31- 60 ml/min. A

deficient proportion of patients (4.8%, n=12) were having CrCl above 90ml/min.

Prevalence of PIMs

According to AGS updated Beers criteria 2019, a total of 62.4% (n=156) patients were prescribed with at least one PIM as identified by Beers criteria 2019. The details of the overall prevalence of PIMs use in older adult patients hospitalized with cardiovascular disease, as specified in the present study, are shown in Table 2. The most common identified PIMs in the study cohort were Proton pump inhibitor, Short-acting insulin according to the sliding scale, Enoxaparin, to name a few. Overall, 8.8% (n=22) of the patients were prescribed with at least 3 PIMs, as described in table 1.

On Bivariate logistic regression, Gender female (OR 2.36, 95% CI 1.36- 4.09; P= 0.002), three diagnosis (OR 4.29, 95% CI 1.31- 14.0; P=0.016), 4 diagnosis (OR 4.8, 95% CI 1.49- 15.44; P= 0.009), 7-9 days of hospital stay (OR 4.74, 95% CI 1.07- 20.96; P= 0.04), 5-8 medications (OR 0.08, 95% CI 0.01- 0.40; P= 0.002), 9 medications (OR 0.09, 95% CI 0.01- 0.50; P= 0.006), CrCl 31- 60ml/min (OR 0.38, 95% CI 0.19- 0.75; P= 0.006), CrCl 61- 90 ml/min (OR 0.15, 95% CI 0.07- 0.32; P= <0.001) were found to be important predictors for the potentially inappropriate prescribing in older adult patients. The predictors analysed for PIMs prescribing are summarised in Table 3.

Discussion

To our knowledge, this is the first study to determine the PIMs use in Indian older adult patients admitted with cardiovascular disease in the medicine/ cardiology department of a tertiary care teaching hospital. This study identified a high frequency of PIMs use in older adult patients according to Beers criteria 2019. It was observed that out of 250 older adult patients, 156 patients had been prescribed with at least one PIM during their entire hospital stay. Inappropriate use of medication is more often occur in older adults as they take multiple drugs simultaneously to treat multiple conditions. A few studies have been conducted worldwide to find out the prevalence of PIMs in CVD, and some studies have reported lower prevalence as compared to our study. On the other hand, few have reported higher prevalence. This difference could be due to a study participant included in different studies, variations in prescribing habits in different countries with different healthcare settings. Another important factor causing variation in the prevalence of PIMs is different criteria used in a different study. In concordance with other studies conducted in different countries, this study's prevalence was lower than that reported by Aguiar et al identified 87.4% of the patients were taking 1 PIM.^[6] On the other hand, a study conducted in Spain by Garcia- Ramos et al. reported a 27.9% prevalence of PIMs in cardiovascular care.^[14]

The most frequently used PIMs in our study were Proton pump inhibitors from independent of diagnosis category as identified by Beers criteria. Proton pump inhibitor (PPI) is the most commonly prescribed drugs and is chronically consumed without an indicated diagnosis. It is necessary that all health care providers monitor the use of PPI in older adults if prescribed for long term as these drugs may increase the risk of clostridium difficile infection, bone and hip fracture.^[15] The second most prescribed PIMs were Insulin Sliding Scale (insulin regimens containing only short or rapid-acting insulin dosed according to current blood glucose levels without concurrent use of basal or long-acting insulin) is an agent approved for diabetic patient. However, in the older adult patients, the older adult patients may have a higher risk of hypoglycaemia without improving hyperglycaemia management.^[16, 17]

According to Beers criteria, Drugs such as diuretics that may cause or exacerbate Syndrome of Inappropriate Antidiuretic hormone secretion and hyponatremia should be used with caution in older adults, especially cardiovascular patients, diuretics are often prescribed to get rid of fluid retention.^[18, 19] Health care providers are advised to keep a close look at sodium level whenever older adults are prescribed with these medications. However, Beers criteria suggest that Aspirin should be used with caution in older adults with age 70.

Nitrofurantoin is first-line therapy for Urinary tract infection. Still, it is considered as potentially inappropriate medication in older adults as these drugs have the potential to cause pulmonary toxicity, hepatotoxicity, and peripheral neuropathy with long term use.^[20]

Long-acting Benzodiazepine was amongst the most commonly prescribed PIMs. As the older adult is mostly suffering from anxiety, depression, and other psychiatric disorders. So, Benzodiazepines are often prescribed to treat these complications in older adults. But Beers criteria recommends that all benzodiazepines should be avoided in older adults as they increase the risk of cognitive impairment, falls, fractures. Moreover, it may worsen the delirium.^[21]

However, age-related significant changes were observed in the kidney function of older adults. Certain medications should be either avoided or their dosage reduced according to the creatinine clearance of the patient. Despite a clear-cut indication, in our study, we have identified 7 PIMs that have been prescribed to 63 older adult patients with CVD. Among them, especially anti-coagulant, was the most commonly prescribed PIMs. Their dosage either should be reduced or avoided according to Creatinine clearance of the patient as they may pose a threat to older adult patients.^[22]

The present study also highlights the predictors of PIMs prescribing in older adult patients with CVD. It was observed that the most important predictors of PIMs prescribing were female gender, three or [?]4 number of diagnosis, 7- 9 days of hospital stay, 5- 8 medications and [?] 9 medications prescribed during their hospital stay, and CrCl of 31- 60ml/min and 61- 90ml/min. These findings results are consistent with the results from previous findings that have reported the same predictors for PIMs prescribing.^[11, 23]

Although the female gender is increasingly perceived as a key predictor of PIMs, systemic gender studies in the older adults patients hospitalized with CVD are still lacking. Compared to male diabetics, the probability of lethal Coronary Heart Disease (CHD) has been reported to be 50% higher in women with diabetes.^[24] the reason for this higher PIMs used in the female older adults with CVD is multifarious and related to India's social structure. Major factors include sluggishness to move to specialists, social bindings/miserliness, non-adherence to treatment plants due to commitment toward family, increase self-medication for ailments, and easy availability of over the counter drugs.^[25]

It was observed that the older adults with 3 or [?]4 numbers of diagnosis/comorbidities are more vulnerable to PIMs use than the population with fewer diagnosis/comorbidities. Several studies have reported a decline in quality of care when patients have multiple morbidities.^[26, 27] several factors contribute to the increased use of PIMs in the older adults with comorbidities. Multimorbid patients tends to have frequent and intensive contact with different specialists' physicians resulting in increased medication prescribing for various conditions.^[28] On the other hand, there is a high possibility of a lack of coordination amongst specialists for different disease prescribing under one roof, leading to the prescription of multiple drugs, which increases the likelihood of PIMs prescription.

Prolonged hospital stays (7-9 days) are one of the main predictors of PIMs use as prolonged hospitalization increases the risk of hospital-acquired infection, increased mortality, economic burden, and poor outcomes in the older adults.^[29] As the hospital stay of the older adults increases, the consultants intend to get the patient out of the disease irrespective of the drug's side effects and adverse effects. Moreover, there is a complete lack of awareness among physicians about the PIMs and Beers criteria.

Patients with deterioration in kidney function are more susceptible to nephrotoxic injury due to the inappropriate dosing of medication.^[30] Moreover, due to the unwanted effects of drugs mentioned in Beers criteria, there is a strong chance of prescribing an inappropriate drug dose that may cause nephrotoxicity in the older adults with altered kidney function.

Nowadays, the older adult is often on polypharmacy/high-level polypharmacy to treat their condition. Furthermore, increased use of drugs in older adult further exacerbates the risk of adverse drug events, drug-drug interactions, and PIMs use. Sometimes, prescribing cascades occur due to the use of multiple drugs.^[8]

In conclusion, the present study results showed a higher prevalence of PIMs in the older adult patients with CVD and females with CVD has emerged as a potential PIM indicator. The study further reflects the need for physician's special attention on polypharmacy/high-level polypharmacy with comorbidities and extended hospital stay due to high risk for PIM. There is a need for compulsory training of physicians at all levels for

the use of Beer criteria for better geriatric health care. Regulatory bodies need to set up geriatric health care desks in tertiary care hospitals to check such PIM incidences to reduce unnecessary economic burden due to infringement in following beer criteria. There is also a strong need to find out disease-wise PIM predictors in a broader range of the populations.

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Figure 1: Prevalence of chronic disease in older adult patients. IVD, Ischemic vascular disease; DCMP, Dilated Cardiomyopathy; CHF, Congestive Heart Failure; HTN, Hypertension; DM, Dilated Mellitus; CKD, Chronic Kidney disease; CLD, Chronic Liver disease; RD, Respiratory disease; PD, Psychiatric disorder;

Table 1: Socio-demographic and clinical characteristics of the older adult patients (n=250)

Characteristics	Frequency	Percentage	Mean (SD)	Median (Minimum-M
Sex	Sex	Sex		
Male	150	60		
Female	100	40		
Age (years)			69 (5)	65 (65- 86)
Educational Qualification	Educational Qualification	Educational Qualification		
Illiterate	168	67.2		
10 th passed	46	18.4		
12 th passed	22	8.8		
Undergraduate	14	5.6		
Smoking	Smoking	Smoking		

Characteristics	Frequency	Percentage	Mean (SD)	Median (Minimum-M
Chronic regular smoker	40	16		
Ex-Smoker	8	3.2		
Non-Smoker	202	80.8		
Alcohol	Alcohol	Alcohol		
Chronic regular alcoholic	38	15.2		
Ex-alcoholic	14	5.6		
Occasional alcoholic	18	7.2		
Non alcoholic	180	72		
No of diagnosis/comorbidities			3 (1)	3 (1- 7)
Length of hospital stay (days)			6 (3)	6 (3- 20)
No of medications			9 (3)	9 (3- 19)
Creatinine clearance (ml/min)			45 (30)	42 (5- 156)

Table 2: Prevalence of Potentially Inappropriate Medication Use in older adults patients with cardiovascular disease

Potentially Inappropriate Medication	No of patients	Recommendation by Beer guidelines	Quality of Evidence	Strength of Recommendation
Independent of diagnosis Omeprazole	Independent of diagnosis 18	Independent of diagnosis Avoid Scheduled use for >8 weeks unless for high-risk patients (e.g., Oral corticosteroids or chronic NSAID use), erosive esophagitis, Barrett’s esophagitis, pathological hypersecretory condition, or demonstrated need for maintenance treatment	Independent of diagnosis High	Independent of diagnosis Strong
Rabeprazole	12			
Pantoprazole	40			
Prazosin	4	Avoid use as an Antihypertensive	Moderate	Strong
Glimepiride	14	Avoid	High	Strong

Potentially Inappropriate Medication	No of patients	Recommendation by Beer guidelines	Quality of Evidence	Strength of Recommendation
Human insulin, according to Random Blood Sugar	52	Avoid (insulin regimens containing only short- or rapid-acting insulin dosed according to current blood glucose levels without concurrent use of basal or long-acting insulin)	Moderate	Strong
Nitrofurantoin	8	Avoid in individuals with creatinine clearance <30mL/min or for long- term suppression	Low	Strong
Chlordiazepoxide	3	Avoid	Moderate	Strong
Trihexyphenidyl	2	Avoid	Moderate	Strong
Zolpidem	3	Avoid	Moderate	Strong
Clonazepam	22	Avoid	Moderate	Strong
Digoxin 0.25mg	4	Avoid this rate control agent as first line therapy for atrial fibrillation	Atrial fibrillation: low Heart failure: low Dosage >0.125mg/day: moderate	Atrial fibrillation: strong Heart failure: strong Dosage >0.125mg/day: strong
Amiodarone	6	Avoid as first- line therapy for atrial fibrillation unless the patient has heart failure or substantial left ventricular hypertrophy	High	Strong
Nortriptyline	4	Avoid	High	Strong
Ketorolac	4	Avoid	Moderate	Strong
Quetiapine	8	Avoid	Moderate	Strong
Clonidine	3	Avoid	Low	Strong

Potentially Inappropriate Medication	No of patients	Recommendation by Beer guidelines	Quality of Evidence	Strength of Recommendation
Ergot mesyloids	2	Avoid	High	Strong
Dependent of diagnosis	Dependent of diagnosis	Dependent of diagnosis	Dependent of diagnosis	Dependent of diagnosis
Delirium				
Ranitidine	3	Avoid	Moderate	Strong
Hydrocortisone	3	Avoid	Moderate	Strong
Drug-drug interaction	Drug-drug interaction	Drug-drug interaction	Drug-drug interaction	Drug-drug interaction
Prazosin + Furosemide	2	Avoid in older women	Moderate	Strong
Urinary incontinence in women				
Hydrocortisone + ketorolac	2	Avoid; if not possible, provide gastrointestinal protection	Moderate	Strong
increased risk of peptic ulcer or GI bleeding				
Drugs that should be used with caution in older adults	Drugs that should be used with caution in older adults	Drugs that should be used with caution in older adults	Drugs that should be used with caution in older adults	Drugs that should be used with caution in older adults
Aspirin for primary prevention of cardiovascular disease and colorectal cancer	12	Use with caution in adults [?]70 years	Moderate	Strong
Furosemide	6	Use with caution as they may exacerbate or cause SIADH or hyponatremia; monitor sodium level closely when starting or changing dosages in older adults	Moderate	Strong
Torseamide	12			
Metolazone	2			
According to creatinine clearance of the patient	According to creatinine clearance of the patient	According to creatinine clearance of the patient	According to creatinine clearance of the patient	According to creatinine clearance of the patient
Creatinine clearance at which action required (ml/min)				

Potentially Inappropriate Medication	No of patients	Recommendation by Beer guidelines	Quality of Evidence	Strength of Recommendation
Enoxaparin <30ml/min	32	Reduced dose	Moderate	Strong
Spirolactone <30ml/min	8	Avoid	Moderate	Strong
Ranitidine <50ml/min	8	Reduced dose	Moderate	Strong
Pregabalin <60ml/min	6	Reduced dose	Moderate	Strong
Gabapentin <60ml/min	2	Reduced dose	Moderate	Strong
Dabigatran <30ml/min	4	Avoid; dose adjustment advised when CrCl >30 mL/min	Moderate	Strong
Trimethoprim-sulfamethoxazole <30ml/min	3	Reduced dose if CrCl 15-29ml/min Avoid if CrCl <15ml/min	Moderate	Strong

NSAID, Nonsteroidal anti-inflammatory drug; SIADH, Syndrome of Inappropriate Antidiuretic Hormone Secretion

Table 3: Predictors of PIM in CVD with comorbidities in geriatric population

Parameters	PIMs present	PIMs absent	AGS Beers criteria 2019 OR (95% CI)	*P-value
Gender				
Male	82	68	1 (reference)	
Female	74	26	2.36 (1.36- 4.09)	0.002
No of diagnosis/comorbidities				
1	6	8	1 (reference)	
2	20	48	0.55 (0.17- 1.80)	0.329
3	58	18	4.29 (1.31- 14.0)	0.016
[?]4	72	20	4.8 (1.49- 15.44)	0.009
Length of Hospital stay (days)				
1-3	12	24	1 (reference)	
4- 6	66	48	1.31 (0.35- 4.86)	0.68
7- 9	54	14	4.74 (1.07- 20.96)	0.04
>9	24	8	1.09 (0.19- 6.11)	0.91
No of medications				
1-4	0	10	1 (reference)	
5-8	38	42	0.08 (0.01- 0.40)	0.002
[?] 9	118	42	0.09 (0.01- 0.50)	0.006

Parameters	PIMs present	PIMs absent	AGS Beers criteria 2019 OR (95% CI)	*P-value
Creatinine clearance (ml/min)				
1-30	76	18	1 (reference)	
31-60	52	32	0.38 (0.19- 0.75)	0.006
61-90	24	36	0.15 (0.07- 0.32)	<0.001
91-120	4	4	0.23 (0.05- 1.03)	0.056
>120	0	4		

**P* < 0.05 indicates significant difference AGS, American Geriatric Society; PIM, potentially inappropriate medications; OR, odds ratio; CI, Confidence Interval

