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Potentially inappropriate medication prescribing among elderly patients with cardiovascular diseases

Moguće neodgovarajuće propisivanje lekova starijim bolesnicima sa kardiovaskularnim bolestima

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Abstract

Background/Aim. The growing number of older adults means higher medicine utilization. The aim of the study was to determine the frequency and identify risk factors of potentially inappropriate medication (PIM) in the elderly population with cardiovascular diseases. **Methods.** The retrospective, cross-sectional study was performed in 2018, and the relevant data were collected during the period from January 2016 to December 2017. The study sample included 1,500 patients over 65 years with cardiovascular disease who had medical records at the Institute for Gerontology and Palliative Care, Belgrade. Assessment of PIM was done by standard international criteria such as the American Geriatrics Society 2015 updated Beers Criteria for PIM use in older adults. **Results.** PIM frequency in the elderly population was 70.3%. In relation to gender, it was more frequent in female elders. The mean number of prescribed drugs was similar for 2016 and 2017, 7.2 and 7.3, respectively. The most common were: medium-acting benzodiazepines (70.9%), central α blockers (23.98%), and antipsychotics (typical and atypical) (20.94%). The most common comorbidity was noted in a group labeled with the International Disease Classification I00-I99, which includes heart and blood vessel diseases [n = 2,658 (36.9%)]. The most common diagnoses belonged to the subgroups I10-I15 [hypertensive diseases, n = 1,298 (18%)], I20-I25 [ischemic heart diseases n = 542 (7.5%)], I30-I52 [other forms of heart disease, n = 705 (9.8%)], I60-I69 [cerebrovascular diseases, n = 94 (1.3%)], and I80-I89 [diseases of veins, lymph vessels, and lymph nodes n = 12 (0.17%)]. The risk factors for PIM were: polypharmacy, gender, nicotine use, cognitive status, nutrition state, and the number of diseases registered in the study sample. **Conclusion.** Cardiovascular diseases in the elderly population are associated with a high prevalence of PIM. Creating health recommendations for prescribing drugs to the elderly that would emphasize these factors could reduce the prevalence of PIM in this population.

Key words:
aged; cardiovascular diseases; drug prescriptions; drug utilization; risk factors; serbia.

Apstrakt

Uvod/Cilj. Sve veći broj starijih osoba koristi lekove. Cilj rada bio je da se utvrdi učestalost i prepoznaju faktori rizika od mogućeg neodgovarajućeg propisivanja lekova (MNPL) starijoj populaciji sa kardiovaskularnim bolestima. **Metode.** Retrospektivnom studijom preseka, sprovedenom tokom 2018. godine, prikupljeni su bitni podaci za period od januara 2016. do decembra 2017. godine. Studijski uzorak obuhvatao je 1 500 bolesnika starijih od 65 godina sa kardiovaskularnim oboljenjima koji su bili korisnici zdravstvenih usluga i imali dostupnu medicinsku dokumentaciju na Institutu za gerontologiju i palijativnu zaštitu, Beograd. Procena MNPL obavljena je upotrebom standardnih međunarodnih kriterijuma poput *American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults*. **Rezultati.** Učestalost MNPL u starijoj populaciji iznosila je 70,3%. U odnosu na pol, veća učestalost MNPL primećena je kod ispitanika ženskog pola. Prosečan broj propisanih lekova bio je sličan za 2016. i 2017. i iznosio je 7,2 i 7,3 lekova, redom. Najviše su propisivani: benzodiazepini sa srednjim vremenom delovanja (70,9%) centralni α blokatori (23,98%) i antipsihotici (tipični i atipični) (20,94%). Najviše komorbiditeta bilo je u grupi bolesti sa međunarodnom klasifikacijom I00-I99 koja obuhvata bolesti srca i krvnih sudova [n = 2 658 (36,9%)]. Najčešće dijagnoze bile su iz podgrupa: I10-I15 [hipertenzivne bolesti, n = 1 298 (18%)],

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I20-I25 [ishemijske bolesti srca, n = 542 (7,5%)], I30-I52 [ostale oblika bolesti srca, n = 705 (9,8%)], I60-I69 [cerebrovaskularne bolesti n = 94 (1,3%)], i I80-I89 [bolesti vena, limfnih sudova i limfnih čvorova n = 12 (0.17%)]. Faktori rizika od MNPL bili su: polifarmacija, pol, upotreba nikotina, kognitivni status, uhranjenost, kao i broj oboljenja zabeležen kod ispitanika. **Zaključak.** Kardiovaskularne bolesti u starijoj populaciji povezane su sa visokom prevalencijom MNPL. Kreiranje zdravstvenih preporuka za propisivanje lekova starijim osobama koje bi naglasile navedene faktore moglo bi uticati na smanjenje prevalencije MNPL u navedenoj popilaciji.

Ključne reči:
stare osobe; kardiovaskularne bolesti; lekovi, propisivanje; lekovi; korišćenje; faktori rizika; srbija.

Introduction

Elderly people are a vulnerable population in a pharmacological sense for two primary reasons: the physiological changes occurring in the elderly population affect and change the pharmacokinetics and pharmacodynamics of the administered drugs, as well as the presence of at least two or more chronic diseases (multimorbidity) [1–3]. The polypharmacy is most commonly present among people aged 65 and over, and it is one of the main causes of the drug-drug or the drug-disease interactions, which results in more frequent adverse drug reactions (ADRs), a poor medicine adherence, faster cognitive decline, unplanned hospitalizations, and higher health costs [4–6]. Now and in the future, increased consequences are expected with population aging and the prolongation of life expectancy.

Many studies have shown a higher risk of drug-drug or drug-disease interaction with the increased number of prescribed drugs. The prevalence of drug-drug interaction in nursing home residents who take two drugs was only 6%, but it significantly rises up to 100% for persons on co-medications with 8 drugs [7], while the probability for drug-disease interaction has the range of 15–40% in frail elderly people [8]. So far, it is generally known the medicines that have the higher potency for the occurrence of ADRs are also widely administered among the elderly. These include non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulants, cardiovascular medicines (including diuretics and statins), antiepileptic drugs (AEDs), benzodiazepines, antibiotics, and oral hypoglycemic agents [8]. Numerous ADRs, as a consequence of drug-drug interaction, can be predicted and prevented by the use of scientific literature, databases, and software for their detection (Lexi-Interact, Micromedex, Drug Interactions, Medscape, and Epocrates) [9].

Moreover, polypharmacy is a significant risk factor leading to potentially inappropriate medication (PIM) prescribing associated with a high rate of disability and mortality (1.6 times higher risk in a more recent systematic review) in the elderly, reducing the quality of life, whether they are in nursing homes or hospitals [10, 11]. The hazard ratio of hospitalization was 1.73 due to the higher prevalence of PIM (ranging between 21.9% and 48%) among elderly nursing home residents in two European counties [12, 13].

PIM was observed in the primary care hospitalized patients but also in community-dwelling older people and nursing home residents [14]. The results of studies conducted both in the outpatient and hospital settings showed that approximately 60% of the elderly use at least one unnecessary medicine. Additionally, the use of the over-the-counter (OTC) preparations and dietary supplements is very common, up to almost 50% in community-dwelling elderly adults. The number of prescribed drugs (more than 9) is increasing in nursing home residents, and the most commonly used drugs were: diuretics, cardiovascular drugs [angiotensin-converting enzyme inhibitors (ACE) inhibitors, calcium channel, and beta-blockers], statins, antipsychotics, benzodiazepines, selective serotonin reuptake inhibitors, and proton pump inhibitors [8].

The prevalence rate of PIM has a wide range in various health settings worldwide, and studies recorded its much higher values in persons living in nursing homes (≈ 45%) compared to the community-dwelling older people (7.5%) [10]. The differences in the used screening tools for its detection and in the quality of prescribing drugs or the status of medication review practices between countries and geographical regions contribute significantly to this [15]. During the last decades, PIM has been a part of the global healthcare concern, and several guidelines worldwide [the Beers criteria, STOPP (Screening Tool of Older Person's Prescription) and START (Screening Tool to Alert doctors to Right Treatment) criteria, PRISCUS, and the Laroche list] provide explicit definitions and lists of PIMs in the geriatric population [16–19]. The Beers criteria was the first published list developed in the twentieth century (1991 by M. Beer) and adapted by the American Geriatrics Society for PIM detection in older people, and up to date, the original list has undergone 5 revisions (the latest in 2019). The original Beers criteria or revised versions with their own health standards are often used worldwide, both in the USA and the European countries [20].

Apart from polypharmacy and multimorbidity in the geriatric population, PIMs are linked with several physician errors summarized as follows: drug prescription without the obvious reason or diagnosis, lack of important information about a patient during prescribing medicines or lack of teamwork between physicians or pharmacists, presence of inaccurate medical records and insufficient knowledge or education about drugs whose prescription should be avoided in the geriatric population [21]. The results of the studies showed that the continuous and more frequent medical education of physicians, pharmacists, and all the medical staff taking care of nursing home residents could be effective and lead to the significant reduction and improvement of the PIM in the geriatric population [22].

According to all available information about the factors that really affect prescribing, it is clear that there is a long list of factors, but it should be emphasized which factor is vulnerable for a specific population such as the elderly, pregnant women, or pediatric patients, etc.

The aim of our study was to present frequencies of PIM in the elderly population with cardiovascular diseases and to identify the factors with a significant impact on PIM present in the study population.

Methods

Study design and *respondents*

The research was designed as an observational, retrospective cross-sectional study conducted at the Institute of Gerontology and Palliative Care (IGPC) in Belgrade and included elderly respondents living in ten Belgrade municipalities. The study was performed for three months in 2018, when data were collected for the period from January 2016 to December 2017. The number of patients who used certain types of health care in this institution for the observed period was 3,131, of which 1,500 patients met the criteria for inclusion in the study sample based on the precisely defined exclusion and inclusion criteria.

The inclusion criteria were: diagnosis of cardiovascular disease, patients' age of 65 or older, who took two or more medications prescribed daily by a medical doctor (MD) at the IGPC, and availability of complete medical documentation with demographic, socio-epidemiological and clinical data on patients.

The exclusion criteria were age below 65 years, patients in the terminal phase of the disease, and incomplete medical documentation.

The study was approved by the Ethics Committee of the relevant health institution, and each respondent was asked to sign an informed consent form to participate in the study before the start of the study. In the case of cognitive disorders, the consent was signed by the closest relatives.

Variables monitored in the study

Relevant data for the patients' analysis were taken from the Helliant electronic database and medical history, and the following data were taken into account: demographic characteristics (sex, age), epidemiological data (education, occupation, nicotine use, drug and food allergies), clinical data, cardiovascular system diseases, cognitive, emotional and nutritional status, as well as data on prescribed medications. The medical documentation was used as a source of information on the functional ability of patients, motivation for rehabilitation, subjective assessment of the health condition, existence of certain functional disabilities (visual and hearing impairment), speech disorders, and information about genetic predispositions.

Information about cognitive status was extracted from the patient's medical record where, according to psychological and psychiatric assessment, patient's cognitive status was noted as normal, with dementia or delirium presence. Besides cognitive status, there was information about emotional status, which was categorized as normal, depression, anxiety, fatigue, or other.

The assessment of nutritional status in the examined population was performed based on body mass index calculated as a quotient of body weight (expressed in kilograms) and body height in square meters.

The prevalence of PIMs in elderly patients was evaluated using explicit criteria, defined by the American Association for the Elderly, Beers Criteria, version 2015 [20].

Statistical analysis

Descriptive statistics, such as percentages and means or median, according to variable nature, were used to describe patient characteristics and to estimate the prevalence of PIM use among the studied population.

Variable normality was assessed by Kolmogorov-Smirnov test. Continuous variables with normal distribution were examined through the Student *t*-test, while Mann Whitney test was used for variables not showing normal distribution. Categorical variables were statistically processed by χ^2 with no comparison for cells, i.e., fields whose values are less than 5 pts, which are not taken into account considering the sample size. The influence of the observed factors on PIM prescribing was determined by a multivariable logistic regression model. The statistically significant value was smaller than 0.05.

The obtained data were analyzed by SPSS software package version 23 [Statistical Package for Social Sciences software (SPSS Inc., version 23.0, Chicago, IL)].

Results

Subject characteristics

The basic characteristics of the sample and the information about the prescribed drugs are shown in Table 1. Regarding the sample size, it included 1,500 respondents, whereby the mean age was 82.7 years, while even 35.6% were older than 85, a very old population. In terms of gender, there was a higher number of females in the study sample compared to the number of males (1,158 vs. 342, respectively).

Polypharmacy was present in a large number of examined participants, both groups (PIM and non-PIM) showed the use of more than 5 drugs. There was a statistically significant difference in polypharmacy between PIM and non-PIM groups.

The distribution of the number of drugs used is shown in Table 1, with the largest number of respondents, as many as 46.7%, using 5 to 8 drugs at the same time. Pronounced polypharmacy (concomitant use of 9 or more drugs) was observed in 31.7% of subjects with PIM. Regarding gender, there was a statically significant difference between PIM and non-PIM groups. The female gender was in a significant correlation with PIM presence.

The cognitive status in the PIM and non-PIM groups clearly indicates a statistically significant difference in

Table 1

Baseline characteristics of study participants

Variables	PIM	Non-PIM	Total	t (χ^2*)	p
Age (years), n (%)					
65–74	194 (18.4)	71 (16.0)	265 (17.7)		
75–84	495 (46.9)	206 (46.3)	701 (46.7)	1.892*	0.387
≥ 85	366 (34.7)	168 (37.8)	534 (35.6)		
Total	1,055 (70.3)	445 (29.7)	1,500 (100.0)		
Gender, n (%)					
male	211 (20.0)	131 (29.4)	342 (22.8)	15.663*	0.000
female	844 (80.0)	314 (70.6)	1,158 (77.2)		
Number of medicines 2016					
mean	7.2	5.2	6.7		
median	7.0	5.0	6.0	11.288	0.000
SD	3.4	3.1	3.4		
Number of medicines 2017					
mean	7.3	5.4	6.8		
median	7.0	6.0	6.0	11.600	0.000
SD	3.3	2.9	3.3		
Number of used drugs, n (%)					
2–4	228 (21.6)	216 (48.5)*	444 (29.6)		
5–8	493 (46.7)	159 (35.7)*	652 (43.5)	122.86*	0.000
> 9	334 (31.7)	70 (15.8)*	404 (26.9)		
Total	1,055 (70.3)	445 (29.7)	1,500 (100.0)	248.06	0.000
Nicotine use, n (%)					
yes	179 (11.9)	53 (3.5)	232 (15.5)	6.060*	0.014
no	876 (58.4)	392 (26.1)	1,268 (84.5)		
Education level, n (%)					
primary school	252 (16.8)	83 (5.5)	335 (22.33)		
intermediate degree	494 (32.9)	183 (12.2)	677 (45.13)		
fifth degree	22 (1.4)	10 (0.6)	32 (21.33)	11.637*	0.040
higher education	56 (3.7)	33 (2.2)	89 (5.93)		
university education	229 (15.2)	124 (8.2)	353 (23.53)		
PhD degree	10 (0.6)	4 (0.2)	14 (0.93)		
Marital status, n (%)					
married	299 (19.9)	136 (9)	435 (29.0)		
divorced	90 (6)	54 (3.6)	144 (9.6)	8.224*	0.042
widower	589 (39.2)	220 (14.6)	809 (53.9		
unmarried	62 (4.1)	50 (3.3)	112 (7.5)		
Nutritional level, n (%)					
normal	876 (58.4)	377 (25.1)	1253 (83.5)		
undernourished	140 (9.3)	37 (2.4)	177 (11.8)	13.416*	0.001
obese	39 (2.6)	31 (2)	70 (4.7)		
Cognitive status					
normal	753 (50.2)	330 (22)	1083(72.2)		
dementia	285 (19)	84 (5.6)	369 (24.6)	3.351*	0.000
delirium	25 (1.6)	23 (1.5)	48 (3.2)		
Emotional status, n (%)					
normal	362 (24.1)	201 (13.4)	563 (37.6)		
depression	227 (15.1)	60 (4)	287 (19.1)	15.685	0.003
anxiety	155 (10.3)	66 (4.4)	221 (14.7)		
fatigue	105 (7)	42 (2.8)	147 (9.8)		
other	189 (12.6)	93 (6.2)	282 (18.8)		
Motivation, n (%)					
high	79 (5.3)	63 (4.2)	142 (9.5)		
usual	563 (37.5)	271 (18)	834 (56.2)	13.395*	0.001
low	396 (26.4)	128 (8.5)	524 (34.9)		
Subjective health assessment, n (%)					
great	36 (2.4)	36(2.4)	72 (4.8)		
very good	24 (1.6)	8 (0.53)	32 (2.1)		
good	284 (18.9)	152 (10.1)	436 (29.0)		
poor	490 (32.6)	214 (14.2)	704 (46.9)	15.990*	0.007
bad	101 (6.7)	27 (1.8)	128 (8.6)		
does not know	102 (6.8)	26 (1.7)	128 (8.6)		

PIM – Potentially inappropriate medication; SD – standard deviation.
The statistically significant value was considered $p < 0.05$.

inappropriate drug prescribing in the group of patients with dementia.

A statistically significant difference was observed in emotional status between the PIM and non-PIM groups, where depression was a condition with a relatively high degree of presence in PIM subjects. A significant difference in the nutritional status was noted between the PIM and non-PIM groups. In these groups, there was a similar number of obese subjects, while the undernourished patients were more frequent in the PIM group.

Comparing the mean age values in the study sample according to PIM presence did not show statistically significant differences.

Analyzing the number of prescribed medicines, by the average number or by category, there is always a statistically significant increase in the number of medicines prescribed in the PIM group of respondents, and that in 2017 compared to 2016 there is a slight increase in the number of prescribed medicines in both groups observed (PIM and non-PIM), although this change was not statistically significant.

Comorbidity of respondents

In addition to the existing basic diagnosis for which they were admitted, the subjects also had accompanying comorbidities. On average, we obtained 4.8 comorbidities in the examined sample. Figure 1 shows the distribution of respondents according to the number of comorbidities. Most subjects (n = 266) had 4 comorbidities with a basic diagnosis.

Table 2 shows the distribution of the respondents' diagnoses. The group I00-I99 includes diseases of the heart and blood vessels, where the most common diagnoses were from subgroup I10-I15.

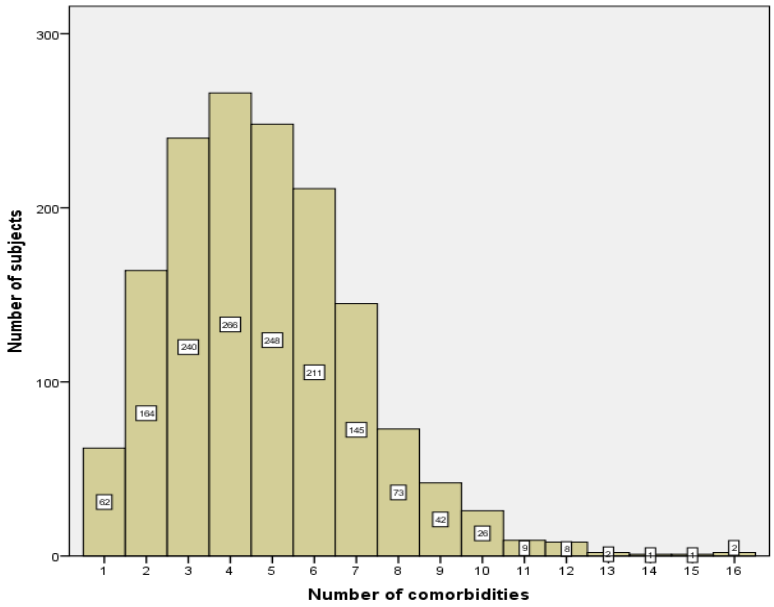

Fig. 1 – Distribution of respondents according to the number of diagnoses.

Table 2

Distribution of respondents according to the diseases diagnoses

Diagnosis	IDC code	n (%) (∑ = 7,199)
Mental disorders and behavioral disorders	F00-F99	1,735 (24.1)
Heart and blood vessel diseases	I00-I99	2,658(36.9)
arterial hypertension	I10	1,298 (18.02)
angina pectoris	I20	501 (6.95)
acute myocardial infarction	I21	16 (0.22)
chronic ischemic heart disease	I25	25 (0.34)
non-rheumatic trefoil disease	I36	4 (0.05)
heart muscle diseases	I42	150 (2.08)
cardiomyopathy	I429	108 (1.49)
atrial fibrillation and ventricular flutter	I48	164 (2.27)
other heart rhythm disorders	I49	169 (2.34)
heart failure	I50	120 (1.66)
brain infarction	I63	33 (0.45)
consequences of cerebrovascular disease	I69	61 (0.84)
phlebitis and thrombophlebitis	I80	12 (0.16)
Diseases of the urinary system	N00-N99	702 (9.8)
Diseases of the endocrine glands, nutrition, and metabolism	E00-E90	506 (7.02)
Diseases of the respiratory system	J00-J99	484 (6.7)

IDC – International Disease Classification.

Table 3

Adjusted analysis for factors associated with PIM

Variables	Wald coefficient	*p*	OR	95% CI for OR	
				lower	upper
Number of drugs	106,135	0.000	0.586	0.416	0.827
Gender	10,711	0.001	1.660	1.225	2.249
Smoking	7.477	0.004	1.511	1.108	2.261
Hypertension	0.251	0.616	1.068	0.826	1.382
Education (year)	2.833	0.726	1.115	0.308	2.037
Subjective health assessment	2.100	0.404	0.125	0.007	2.264
Motivation	1.482	0.477	0.687	0.375	1.260
Emotional status	2.050	0.133	1.149	0.783	1.685
Cognitive status	7.303	0.026	2.464	1.228	4.944
Marital status	4.122	0.249	1.341	0.654	2.749
Nutrition	15,358	0.000	4.108	2.025	8.333
Number of diseases	8.114	0.002	3.992	2.716	5.105
Constant	0.094	0.759	1.324		

Hosmer and Lemeshov χ^2 was 11.718; $p = 0.164$; Cox&Snall R^2 was 0.166 and Nagelkerke R^2 was 0.250.
OR – Odds ratio; CI – confidence interval.
The statistically significant value was considered $p < 0.05$.

Logistic regression analysis clearly indicates the influence of a number of diseases on PIM presence in the examined population (Table 3).

Potentially inappropriate drugs according to Beers criteria

The total number of PIMs determined by the Beers criteria was present in 1,055 (70.3%) subjects compared to prescribing adequate drugs in 445 (29.7%) subjects. Figure 2 shows the distribution of respondents according to the number of PIMs. The largest number of respondents, as many as 577 (38.4%), had 1 PIM, 305 (20.3%) respondents had 2, while 142 (9.5%) respondents had 3 PIMs. Subjects had an average of 1.2 PIMs in therapy during the year (range of 1–8).

Analyzing the pharmacological subgroups inducing PIM in our sample showed that the most common drug classes were short and medium-acting benzodiazepines (in 70.9%), antipsychotics (typical and atypical) (in 20.94%), and central α blockers (in 23.98%). Concerning gender, there was no statistical difference. The only significant differences by gender were reported for bromazepam (higher in female subjects; $\chi^2 = 11{,}931$; $p = 0.000$) and in doxazosin, where a higher number (3.3%) of male respondents received this drug (Fisher test, $p = 0{,}041$). In the benzodiazepines group, short and middle-acting benzodiazepines showed the highest rate of PIM prevalence, where bromazepam had the highest rate, even 49.8%, followed by lorazepam in 23.9% of PIM subjects. Long-acting nonbenzodiazepines were not present in so many cases; diazepam was found in 9.6% of PIM subjects.

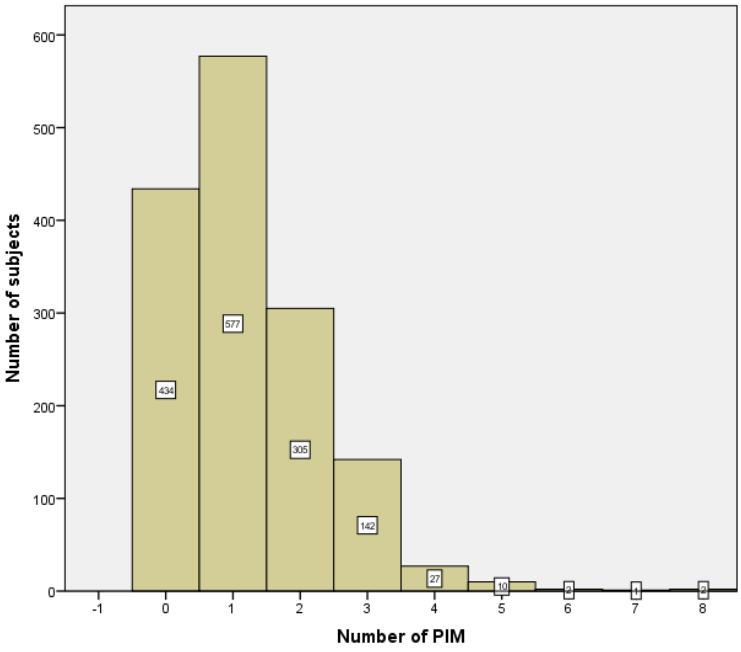

Fig. 2 – Distribution of respondents according to the number of potentially inadequate medication (PIM).

In order to identify factors associated with PIM, multiple logistic regression was conducted (Table 3) that examined the influence of 28 different variables, of which even 11 had statistical significance. After the adjustment, factors identified as significant for PIM in the elderly population by the logistic analysis were polypharmacy, gender, nicotine use, cognitive and nutritional status, and a number of diseases (Hosmer and Lemeshov χ^2 was 11.718; p = 0.164; Cox&Snall R^2 was 0.166 and Nagelkerke R^2 was 0.250).

Discussion

Reduction and timely prevention of PIM prescribing in elderly patients can significantly affect the health care approach and improve clinical and economical results for this specific vulnerable group. Specific pharmacological and pharmaceutical approach is necessary for these patients, and additional monitoring after drug administration is of great importance and creates a field of need for continuous monitoring of desired/adverse events in this area. The routine use of specific tools for PIM identification should become an unavoidable component of health care policy in most countries with a high prevalence of polypharmacy which is, according to literature-based evidence, one of the most important prediction factors [21–25]. Previous research of PIM in our country was not based on Beers criteria as specific tools but showed a relatively high prevalence of PIM; the study from 2014 [23] showed 27.3% of PIM, while data from 2016 [26] indicated a higher value, even 41.3%. To our knowledge, this is the first study in our country that used Beers criteria version 2015 for PIM research in elderly patients, which can bring significant results to the professional and general public, especially due to the specific modification of this version compared to the older versions from 2012 or 2011.

Our results clearly point to the alarming facts about PIM among the elderly population, even 70.3% with PIM prevalence. This high value was most frequent in female patients (Table 1). An interesting observation was that the average number of prescribed medications was similar during the two years, 7.2 and 7.3, respectively. The presence of polypharmacy was in accordance with the above data for both years. In 2016, even 827 patients out of 1,500 had concomitant use of 5 or more drugs, while significant polypharmacy (use of ≥ 9 drugs) was present in 40.4% of the mentioned number of patients. Similar observations were for 2017; polypharmacy was present in 834 patients, i.e., 39.92%. The significance of mentioned variables has been proven by multivariate logistic regression, where gender was characterized by adjusted odds ratio (OR) 1.660 and polypharmacy category with adjusted OR 0.586. The polypharmacy category of used drugs showed as a protective factor which can be explained by the more careful approach by doctors in a specific population such as elderly community-dwelling patients. The presence of polypharmacy as a predictor factor of PIM has been observed in numerous clinical studies. However, an interesting observation was made regarding data from Serbia. The data show that this factor was protective in our study in contrast with the earlier data, where it was the risk factor [adjusted OR 2.85, 95% confidence interval (CI) 1.97–4.14 from 2014 study and 3.05, 95% CI 1.59–5.85] [23, 24]. Our findings are not surprising, considering the research chronology of PIM in the elderly in our country and the consequent growing awareness of medical doctors after this research. On the other hand, there is a large pool of biomedical evidence in conflicting reports on polypharmacy effect on PIM, and further cross-sectional national study will further clarify this topic in detail in different geographic areas in Serbia [26–28].

The presence of polypharmacy as a PIM significant factor in our study is somewhat unexpected due to the presence of a large number of comorbidities at the level of the entire study population and due to the relatively high average number of comorbidities per subject, as much as 4.8. It should be emphasized that 2 cases were recorded where the subjects had 16 comorbidities, which can significantly affect the caution and reservations of physicians when defining a therapeutic approach for such patients. According to this data from our research, we should point out a very important observation – the influence of the number of diseases on PIM presence in the study sample. Multivariable logistic regression showed a strong influence of this factor and presented a significant risk factor through an adjusted OR value of 3.99. This can be explained by a large number of medical specialist examinations of patients with comorbidity and consequently the simultaneous prescribing of drugs that enter into potential interactions according to Beers criteria [22, 25–29].

The study result in our research point out women as a specific risk factor for PIM (adjusted OR 1.660, 95% CI 1.225–2.249). Females are probably more prone to PIM due to the longer life expectancy of the female population worldwide, which many national-wide socio-epidemiological studies noted, and consequently the higher number of medical conditions that can develop due to physiological and pathophysiological processes due to aging. In line with our results, there are many studies with the same conclusion in terms of gender as a risk factor for PIM [27–29].

According to the obtained results, benzodiazepines are the most common PIM in the examined elderly population. Inappropriate use of benzodiazepine in elderly people inevitably leads to the increase in adverse effects, such as increase of sedation effects, and in rare cases results in depression of the cardiovascular and respiratory centers. Numerous information based on literature clearly points out a positive correlation between benzodiazepine use and the high rate of morbidity and mortality among elderly patients [30, 31]. As our study group was created based on the presence of cardiovascular diseases, it is very important to emphasize the significance of the awareness of benzodiazepine prescribing in community-dwelling elderly people with this disease. Benzodiazepine adverse effects derived from PIM can affect not only individuals but also families and society, which can present a great economic cost for the whole mentioned subpopulation.

The majority of studies reported prescription of PPI (proton pump inhibitors) and NSAID besides prescription of benzodiazepine as the most common PIM factor [27–29], contrary to our reports. A possible explanation for this inconsistency can be the increased awareness of doctors about the liquid retention by NSAIDs which can induce exacerbations of cardiovascular disease. For other inconsistencies concerning the PPI drugs, there is no logical justification, thus further clinical analysis may bring us some reasonable explanation.

The use of antidepressants as a PIM category in the study population was expected due to the presence of depression in 19.13% of subjects, which was a higher frequency compared to other mood disorders. The results of research on the use of anticholinergics in elderly patients clearly indicate a positive correlation with outcomes such as reduced cognitive ability and the occurrence of dementia [32]. These data correlate with our results where the presence of dementia in the group of subjects with PIM was 19% compared to non-PIM subjects with dementia in only 5.6% of subjects. Due to the stated reasons, physicians must avoid prescribing psychotropic drugs in the population of elderly patients.

Paroxetine as the antidepressant drug turned out to be inappropriate in our research, according to Beers criteria, in as many as 51 patients. This antidepressant agent should be avoided among elderly people because of the higher risk of mortality outcome, which is the conclusion of different epidemiological studies [28, 29, 33]. Our results for typical and atypical antipsychotics indicate a relatively high incidence of their use which is not an adequate approach according to Beers criteria, where quetiapine has the highest rate in as many as 109 patients.

In the additional pharmacological group, which included an inappropriate medication for our subjects according to Beers criteria, were antipsychotics. The higher incidence of death followed the use of antipsychotics due to pneumonia has been reported, where atypical antipsychotics have a higher rate than the typical ones [34]. The most frequently prescribed antipsychotic was quetiapine (10.33% of the PIM population), which is in accordance with the national cross-section study conducted among the Norwegian population [35]. There was scientific debate about the increase of cardiovascular risk in a patient undergoing antipsychotic therapy, but up to now, there are no scientific data that strongly indicates this correlation and specific guidelines for unsafe use of antipsychotic drugs by patients with cardiovascular diseases [36]. However, medical experts should keep in mind the recommendation of the Beer criteria, which says: “Antipsychotics are associated with great risk of cerebrovascular accident (stroke) and mortality in persons with dementia” [16].

Cardiovascular diseases are one of the leading causes of death, according to the World Health Organization. As many as 31% of all deaths worldwide are caused by these diseases. Heart attack and stroke are on the pedestal of cardiovascular events related to lethal outcomes, while hypertension is the most common chronic non-communicable disease in this group. As many as 1.13 billion people in the world have this diagnosis [37]. As the use of certain medications can affect the consequent increase in the risk of cardiovascular events, it is especially important to monitor the administration of such drugs in persons diagnosed with cardiovascular disease. The beneficial clinical effects of multiple drug therapy are often overshadowed by the side effects they cause on both the underlying disease and other organ systems, so falls and consequent fractures are common with inappropriate cardiovascular therapy [38, 39].

Nicotine use is recognized as a risk factor for numerous health conditions in different populations, specifically in the elderly population, due to their physiological and pharmacological differences, which can reflect the administered therapy and the consequently achieved therapeutic goals. Most health professionals know that nicotine induces the activity of liver enzymes P450 isoform 1A2 and 2B6 [40], as these two forms are involved in the metabolic pathway of the drugs from antidepressants and antipsychotics groups. This should alert their prescription to persons using nicotine daily.

The two potential risk factors for the PIM in the elderly are cognitive status and nutrition. The cognitive status in our study was defined as a risk factor with an OR value of 2.464, which induces cognitive impairment when a healthcare professional selects one or more drugs affecting the central nervous system activity. The research has shown that specific nutritionals associated with the reduction of certain cardiovascular risk factors have a protective effect on cognitive status and prevent the development of dementia in the elderly [41, 42]. There is also evidence in references confirming an inversely related correlation between nutrition status and the number of used drugs that can be correlated with our result. This can be explained by bad habits of elderly people presented by the lower intake of specific vitamins (such as A, D, E, and B vitamins) and a higher intake of cholesterol, glucose, and sodium, which can lead to the development of numerous cardiovascular diseases and consequently produce the need for the drugs prescribing in large amounts [43, 44]. According to these scientific facts, our result, highlighting nutrition status with adjusted OR 4.10, presents valuable information for health care professionals.

It should be emphasized that there were specific limitations in our research. First, the study design had a retrospective character. Secondly, we used the 2015 Beers Criteria for PIM assessment, and that is not the last version of this PIM tool. The last revision was done in 2019 when some drugs were added while others were eliminated regarding the 2015 one, but when we started the data collection (2018) this was the most often used version. An additional limitation was the cross-sectional design of the study, which could not determine the real causality between factors and outcomes but could indicate the most significant points.

Conclusion

Our study suggests that elderly patients are more prone to PIM prescription due to several risk factors on which health professionals should be focused during the health assessment of this vulnerable patients group. Moreover, the results of this study point out how the Beer criteria can be a

useful tool and highlight the importance of their further integration into health policy. Healthcare education and widespread dissemination of the Beer criteria should be imperative as a potential method for a better health approach and the resulting quality of life for elderly people.

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