Survival of hospitalized older adults with prior use of potentially inappropriate medicine

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Abstract

Objectives: We aimed to evaluate the impact of potentially inappropriate medications prescribed prior to hospitalization (PIM-ph) on the mortality of hospitalized older adults. Methods: We included 318 patients, aged ≥65 who sought emergency care and were hospitalized for any clinical reasons. Information on patients' clinical and social indicators was obtained via structured interviews conducted 24 to 48 hours after hospitalization. All medications used by older adults prior to hospitalization were recorded, and PIM-ph were identified using the Brazilian PIM Consensus. The study considered the influence of the entire set of PIM-ph and specific PIM-ph used by these patients. The impact of PIM-ph use during hospitalization and after 30 days of this event was statistically determined by multivariable Cox proportional hazard regression analysis, which included sex, age, and other clinical and functional indicators as intervening variables. Results: The prevalence of PIM-ph use was 49.7% (n=158). A total of 85 (26.7%) patients died during hospitalization or within 30 days after discharge. Eighteen pharmacological classes of PIM-ph use were identified. The use of total PIM-ph, benzodiazepines (IC: 1.055-3.365, p= 0.032), digoxin(IC: 1.623-7.048, p=0.001), and loop diuretics (IC: 1.000-3.455, p=0.05) increased the relative risk of mortality independent of sex, age, clinical causes of hospitalization, frailty risk, social support, presence of confusion symptoms, polypharmacy, and in-hospital evolution of geriatric complications. Conclusion: PIM-ph use, especially benzodiazepines, digoxin, and loop diuretics, could contribute to mortality risk in hospitalized older adults. These results could be relevant in the management and therapeutic care of hospitalized patients.

Keywords: Aged. Hospitalization. Potentially Inappropriate Medication. Mortality.

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INTRODUCTION

The management of hospitalized older patients is highly complex, probably associated with heterogeneous biological aging processes and non-specific complications, including mobility impairment, fall history, cognitive impairment, and drug iatrogenic[1,2]. These complications are known as geriatric syndromes, a term broadly used by geriatricians and gerontologists to highlight the unique features of common health conditions in the elderly[3]. In addition, aging-induced physiological changes could influence the efficacy and safety of certain drugs contributing to iatrogenic in older adults. Therefore, a pharmacological prescription is considered a component that directly affects health management in older adults. Choosing the appropriate medication for each clinical condition must combine the requirement for effectiveness and low risk of adverse effects to achieve a good cost-benefit ratio[4].

As older people exhibit modifications that can alter the pharmacokinetics of many drugs, in recent years, efforts have been made to identify potentially inappropriate medicines (PIM) used by this age group. PIM refers to medications that carry a higher risk of adverse effects when given to older adults or in certain medical conditions. These medications may be considered inappropriate due to the unfavorable risk-benefit ratio or a higher risk of side effects when compared to other available medications. PIMs can cause adverse drug reactions, falls, cognitive impairment, and other complications, particularly in older adults who are already at an increased risk of drug-related problems. Several criteria have been developed to identify PIMs, such as the Beers Criteria by the American Geriatrics Society and the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) criteria.[4,5] The use of these criteria can help healthcare providers to identify PIMs in older adults and adjust medication therapy accordingly. By reducing the use of PIMs, healthcare providers can improve medication safety and reduce the risk of drug-related problems in older adults.[4,5]

Bories et al.[5] estimated that the prevalence of PIM in primary care, home care, and hospital care was 19.1%, 29.7%, and 44.6%, respectively. Another review, which included information from five databases, also described that 57.9% of older adults have some PIM prescription[6]. The PIM in 458 older patients from Brazilian primary healthcare was estimated to be 44.8%[7]. PIM use has also been associated with polypharmacy and dementia in institutionalized older adults, such as benzodiazepines (BDZ) drugs[8]. A cohort ten-year follow-up study that included 418 Brazilian older adults reported a PIM incidence of 44.1 cases per 1,000 people per year with a relevant impact on mortality[9].

Furthermore, PIM prescription has been associated with the evolution of geriatric complications, delirium, seeking medical care after hospital discharge and hospital re-admission, need for surgical intervention, increased mortality of cancer patients, and higher risk of institutionalization and death of older adults [10-17].

However, studies on PIM use generally focus on their adverse effects that can lead to hospitalization, institutionalization, and death. Therefore, the aim of this study is to investigate whether the use of PIM before hospitalization could impact the hospital clinical outcome and the risk of death of patients.

METHODS

Study design and population

An observational, longitudinal, prospective, and descriptive population-based study was conducted from September 2015 to October 2016 in older adults admitted to the hospital from the emergency room at the University Hospital of the Federal University of Santa Maria (HUSM), Santa Maria, Rio Grande do Sul State, Brazil.

In developing countries, such as Brazil, older adults are 60 years of age or older, representing 14,79% of the population in 2021[18]. For this reason, the research investigation was initially designed to include individuals aged 60 years and over. However, as most experiments involving PIM use have been carried out in individuals aged 65 years and around, we decided to exclude those younger from the sample in this study. Therefore, we selected 318 subjects using a simple random sample based on sample size

calculation performed for a cohort study, taking into account the incidence of hospitalizations of the elderly in Brazil in 2015, of 2.669,949, for a confidence level of 90% and 5% margin of error. The incidence of variables associated with death and hospitalization of adults in the emergency room, based on data provided in the HUSM Statistics Section. They were 65 years or older at the time of their inclusion in the study. General exclusion criteria included insufficient information about medication use before admission or lack of consent to participate in the study. All elderly people who stayed less than 24 hours in the emergency service were also excluded, thus making it impossible to collect the information necessary to conduct the study.

The following patient approach and follow-up flow were used in the study: (i) older adult people sought emergency care at the hospital; (ii) all patients referred for hospitalization were invited to participate in the study; (iii) detailed information about the patient's clinical and social indicators, including the use of some clinical geriatric tools, were applied by trained health professionals or graduate students between 24 and 48 h after hospitalization; (iv) during hospitalization all participants were accompanied by the geriatric doctor that is an author in this study; (v) a survey was conducted about all the medications the patient ingested before hospitalization; (vi) further prescribed drugs were databank plotted and the identification of PIM-ph use was performed based in the Brazilian consensus of potentially inappropriate medication for elderly people (I, which was based in the American Geriatrics Society Beers Criteria and in the STOPP/START criteria[19,20]. The analysis considered the influence of the entire set of all PIM-hp and specific PIM-ph used by patients; (vii) after organizing the database in PIM-ph patients and patients without PIM-ph use (here identified as control individuals) were compared regarding sex, age, some pre-hospitalization social and health indicators. Detailed information about the patient's clinical evolution in the hospital was obtained from the medical records. Patient survival up to 30 days after hospital discharge was assessed by telephone contact with the older adult or caregiver; (viii) a multivariate analysis was performed to identify potential covariates that could influence the impact of PIM-ph use on the survival of hospitalized older adults.

Ethical statement

This study is part of the "Development of a line of care for the older hospitalized adults at the University Hospital of Santa Maria" research project approved by the Research Ethics Board of the Federal University of Santa Maria and registered on the Brazil Platform (Approval opinion number 3.498.206). The study also included older people with a lowered level of consciousness or with clinical conditions that affected their cognition. Therefore, all patients or their caregivers provided informed consent.

Pre-hospitalization social and health descriptive variables

The main descriptive variables of the study were age, sex, the clinical condition that led to hospital admission, and results from four tools widely used in geriatric clinics and, previously validated in Brazilian Portuguese Language: Identification of Seniors at Risk (ISAR)[21], Charlson Comorbidity Index (CCI)[22], Confusion Assessment Method (CAM)[23], Geriatric Depression Scale (GDS-4)[24]. The ISAR[21] score is a valuable screening tool for frailty and identifies elderly patients at risk of adverse outcomes after an emergency department (ED) visit. The instrument is an assessment of 6 yes/no items that cover the area of need of help (2 items), prior hospitalizations, sensory restrictions (vision), cognitive impairment, and multimorbidity (polypharmacy). An ISAR score higher than two points is considered positive for geriatric risk factors[21]. The CCI consists of 17 comorbidities, divided into 19 clinical situations with scores between 1 and 3; the sum indicates the chance of survival for one year[22]. CAM score 23 is composed of four attributes related to cognitive function: (1) mental confusion with acute onset and fluctuating course, (2) inattention, (3) disorganized thinking, altered level of consciousness, and (4) delirium symptoms. The diagnosis of delirium is confirmed when both items “1” and “2” and one of the items “3” and “4” are present. The GDS-4 evaluates indicators of Geriatric Depression; the score on this scale ranges from 0 to 4 points, and a score equal to or less than 1 point indicates depression[24].

In addition to these scales, information about the following clinical and functional variables presented

before hospitalization were also collected by trained researchers and evaluated here: older persons in need of caregiver support, living arrangements, social support, previous hospitalization in the last year, polypharmacy (five or more drugs daily used), body weight loss in the previous six months before hospitalization; urinary/fecal incontinence, delirium, immobility, main clinical conditions associated to hospital admission diagnosed by International Classification of Diseases (ICD-10)[25] that was in force during the period in which the study and data analysis were carried out. The in-hospital evolution of clinical and functional complications (delirium, immobility, urinary/fecal incontinence, nosocomial infection) was also evaluated.

Outcomes

The primary outcome measure was older adults' mortality, including those who died while hospitalized and those who died within 30 days of hospital discharge with and without PIM-ph use.

Statistical analysis

Descriptive statistics were presented as counts (n) and relative frequencies (%), mean ± standard deviation (SD), or median and 95% confidence interval according to variable type (quantitative or categorical). The interquartile range was used as a measure of median dispersion. Normal distribution previously determined by Kolmogorov-Smirnov test. The survival analyses were performed with multivariable Cox proportional hazard regression model analysis. The potential intervening variables included in the multivariate analysis were sex, age, and clinical and functional variables that showed significant differences between PIM-hp and controls. The significance level considered for the inclusion of variables in the model was $p<0.10$. In addition, the clinical diagnosis associated with hospitalization, and polypharmacy were included in the multivariate analyses. The proportional hazard assumption was checked, and the models were stratified as needed. The mean survival curves and relative risk estimates with 95% confidence intervals (CIs) were plotted using multivariable Cox regressions. In order, to compare two survival curves, the log-rank test was used. Statistical significance was set at $p<0.05$.

RESULTS

The mean age of the 318 older adults included in the study was 74.6 ± 7.6 years, median = 73 years (minimum = 65, maximum = 96 years). There were 169 (53.1%) males and 149 (46.9%) females. A total of 85 (26.7%) patients died during hospitalization or 30 days after hospital discharge. The prevalence of PIM-ph was estimated at 49.7% (n = 158). The baseline characteristics, functional and health pre-hospitalization indicators, evolution of in-hospital complications, and mortality were compared between PIM-ph and controls (Table 1).

PIM-ph group presented patients with less continued home support and a higher frailty risk (ISAR test) than controls. The other variables were similar between the two groups. In the PIM-hp group, 21 drugs listed in Table 2 were identified.

Among PIM-ph drugs identified here, at least five have their pharmacological action on the central nervous system (CNS). The most prevalent use of CNS drugs were benzodiazepines (BDZ) and antidepressants (serotonin inhibitors or tricyclics drugs). Others, such as opioids, sedatives, and barbiturates, were less prevalent in the patients included in this study. The main PIM-ph used by older adults in treating cardiovascular diseases were digoxin and loop diuretics. None of the PIM-ph used by less than ten patients were included in isolated analyses as they would not allow more consistent multivariate analyses.

Table 1. Comparison between Brazilian older adults with potentially inappropriate use of drugs before hospitalization (PIM-ph) and controls of baseline characteristics, functional/clinical pre-hospitalization indicators, the evolution of in-hospital complications, and mortality. Santa Maria, RS, 2023.

Variables		PIM-ph Use n (%)	Controls n (%)	*p*
Sex	Male	80 (47.3)	89 (52.7)	
	Female	78 (52.3)	71 (47.7)	0.372
Age groups (years)	65-69	47 (29.7)	50 (31.3)	0.137
	70-74	46 (29.1)	46 (28.8)	
	75-79	18 (11.4)	32 (20.0)	
	80-84	21 (13.3)	13 (8.1)	
	> 85	26 (16.5)	19 (11.9)	
Need caregiver		31 (19.9)	35 (22.0)	0.641
Living arrangements	Living alone	13 (8.2)	21 (13.2)	0.315
	Living with someone	143 (90.5)	136 (84.9)	
	Institutionalized	2 (1.3)	3 (1.9)	
Social support				
	Continued home-support	67 (42.4)	93 (58.1)	0.005
	Sporadic home-support	25 (15.8)	28 (17.5)	
	No home support	66 (41.8)	39 (24.4)	
Pre-hospitalization social and health indicators				
Previous hospitalization (one year)		63 (40.9)	52 (32.9)	0.143
Higher frailty risk (ISAR test)		96 (60.8)	68 (42.5)	0.001
Charlson Comorbidity Index (CCI)	One year survival chance			0.313
	98 %	23 (14.6)	28 (17.5)	
	89 %	60 (38.0)	72 (45.0)	
	79%	49 (31.0)	42 (26.3)	
	64%	26 (16.5)	18 (11.3)	
Confusion symptoms (CAM test)		14 (9.1)	6 (3.9)	0.064
Depressive symptoms (GDS-4 score)		69 (53.5)	73 (51.0)	0.688
Polypharmacy (≥ 5 drugs/day)		13 (8.2)	14 (8.8)	0.867
Loss body weight in the last 6 months		53 (33.5)	42 (26.3)	0.155
Urinary incontinence		52 (32.9)	44 (27.5)	0.293
Immobility		37 (23.4)	29 (18.1)	0.054
Main clinical conditions associated to hospital admission [a]				0.562
	Stroke	29 (18.4)	25 (15.6)	
	Cancer	24 (15.8)	33 (20.6)	
	Lung diseases	12 (7.6)	15 (9.4)	
	Gastrointestinal conditions	31 (19.6)	21 (13.1)	
	Infectious diseases	12 (7.6)	12 (7.5)	
	Trauma	29 (18.4)	37 (23.1)	
	Others	20 (12.7)	17 (10.6)	

to be continued

Continuation of Table 1

Variables	PIM-ph Use n (%)	Controls n (%)	*p*
Clinical and functional evolution during hospitalization			
Complications	88 (55.7)	78 (48.8)	0.215
Delirium	29 (18.4)	24 (15.0)	0.577
Immobility	77 (48.7)	66 (41.3)	0.054
Urinary/fecal incontinence	10 (6.3)	16 (10.0)	0.277
Nosocomial infection	28 (21.2)	22 (15.9)	0.265
In-hospital death	44 (27.8)	20 (12.5)	0.001
Death after hospital discharge	15 (13.5)	6 (4.7)	0.017
Total deaths	59 (37.3)	26 (16.3)	0.0001

[a]Diagnosed according to the International Disease Classification (ICD-10).

Table 2. Main potentially inappropriate medications used previously hospitalization (PIM-ph) by Brazilian older adults admitted to a hospital from the emergency room.

Drugs used before hospitalization by different body system targets	
Drug	n (%)
Nervous system	115 (72.0)
Antidepressants (Serotonin inhibitors, tricyclics) drugs	49 (15.4)
Benzodiazepines (BDZ)	32 (10.1)
Tricyclic antidepressants	8 (2.5)
Barbiturates/sedatives	5 (0.9)
Antipsychotics	3 (0.9)
Opioids	5 (1.6)
Other	13 (4.1)
BDZ plus Antidepressants	11 (3.5)
Cardiovascular system	64 (40.5)
Digoxin	15 (4.7)
Loop diuretics	29 (9.1)
Nifedipine	03 (0.9)
Other	17 (5.3)
Endocrine system	15 (9.5)
Glibenclamide	11 (3.5)
Corticoids	1 (1.9)
Other	3 (0.9)
Gastrointestinal system	7 (4.4)
Mineral oil	4 (1.3)
Other	2 (0.5)
Musculoskeletal system	7 (4.4)
Non-steroidal anti-inflammatory drugs	5 (1.6)
Other	
Nitrofurate	2 (0.6)

to be continued

Continuation of Table 2

In-Hospitalization used drugs	
Drug	n (%)
Antithrombotics/Anticoagulants	71 (22.3)
Antibiotics use	
Beta-lactam antibiotics	59 (18.6)
Nucleic acid synthesis inhibitors	17 (5.3)
Beta-lactamase inhibitors	18 (5.7)
Protein synthesis inhibitors	11 (3.5)
Glycopeptides	2 (0.6)
Cell membrane inhibitors	1 (0.3)

The influence of sex, age, leading functional and clinical indicators on survival of the hospitalized older adults from an emergency room was determined (Table 3). In the multivariate analysis, the following potential intervenient variables were included: sex, age, risk of frailty estimated by the ISAR test, previous existence of social support to an older adult patient, confusion symptoms measured by CAM test, and in-hospital evolution of geriatric complications. We also inserted in the multivariate model the ICD-10 clinical diagnosis at admission and polypharmacy prior hospitalization. These variables were selected from the univariate analyzes described in Table 1. However, as the Charlson test estimates the percentual chance of survival from variables already included in other scores tested here, we did not have this indicator as a potential intervening variable in the multivariate analysis that evaluated the association between PIM-ph use and older adults' mortality.

The general PIM-ph uses considering the whole of all drugs prescribed to older adults included in the study was significantly associated with lower in-hospital survival and death until 30 days after hospital discharge independent of all intervening variables included in the multivariate model. In addition, the specific use of BDZ, digoxin, and Loop diuretics was also independently associated with a lower survival rate in older adults (Table 3, Figure 1).

Table 3. Multivariate Cox regression analysis of mortality relative risk of Brazilian older adults hospitalized from the emergency room.

Variables		Deaths n (%)	RR	95% CI Upper-Lower	*p*
Sex	Female	39 (26.2)			
	Male	46 (27.2)	1.004	0.655-1.538	0.987
Age (years)	65-79	85 (23.4)			
	≥ 80	29 (36.7)	1.818	1.157-2.856	**0.010**
Functional and Clinical variables					
Frailty Risk (ISAR test)	Lower	33 (21.4)			
	Higher	52 (31.7)	1.451	0.933-2.255	0.098
Survival chance (CHARLSON test)	98%	05 (9.8)			
	89%	30 (22.7)	2.181	0.841-5.669	0.109
	79%	26 (28.6)	2.718	1.008-7.331	**0.048**
	64%	24 (54.5)	5.809	2.185-15.445	**0.0001**

to be continued

Continuation of Table 3

Variables		Deaths n (%)	RR	95% CI Upper-Lower	*p*
CAM-S test	No	67 (23.3)			
	Yes	10 (50)	2.470	1.215-5.023	**0.013**
GDS test (depressive symptoms)	No	27 (20.8)			
	Yes	36 (25.4)	1.179	0.708-1.964	0.526
Polypharmacy	No	77 (26.6)			
	Yes	08 (29.6)	1.085	0.521-2.226	0.828
In-hospital Complications	No	28 (18.4)			
	Yes	57 (34.3)	1.858	1.174-2.940	0.008
In-hospital antibiotics use	Yes	21 (29.6)	1.193	0.728-1.953	0.484
	No	64 (25.9)			
Use of PIM-ph by older adults (n = 158)[a]					
All PIM-ph[a]	No	26 (16.3)			
	Yes	59 (37.3)	2.269	1.416-3.635	0.001
Benzodiazepines	No	70 (24.6)			
	Yes	15 (44.1)	1.884	1.055-3.365	0.032
Antidepressives[b]	No	74 (27.6)			
	Yes	10 (20.4)	2.391	0.766-2.961	0.235
Opioids	No	82 (26.2)			
	Yes	03 (60.0)	1.687	0.703-8.128	0.163
Digoxin	No	76 (25.1)			
	Yes	09 (60.0)	3.382	1.623-7.048	0.001
Loop diuretics	No	72 (24.9)			
	Yes	13 (44.8)	1.858	1.000-3.455	0.05

RR = relative risk. CI 95% = confidence interval 95%. The estimated RR of death was determined by multivariate Cox proportional hazard regression inserting covariates in the model. (a) The analysis of PIM-ph (all or specific medicines) impact on RR to dead was corrected by the following covariates: sex, age, frailty risk determined by ISAR test, the existence of social support, presence of confusion symptoms evaluated by CAM test and in-hospital evolution of geriatric complications. The diagnosis of diseases identified by the ICD-10 and polypharmacy (>5 daily medicines) was also included in the model. (b) Serotonin inhibitors plus tricyclic antidepressant drugs.

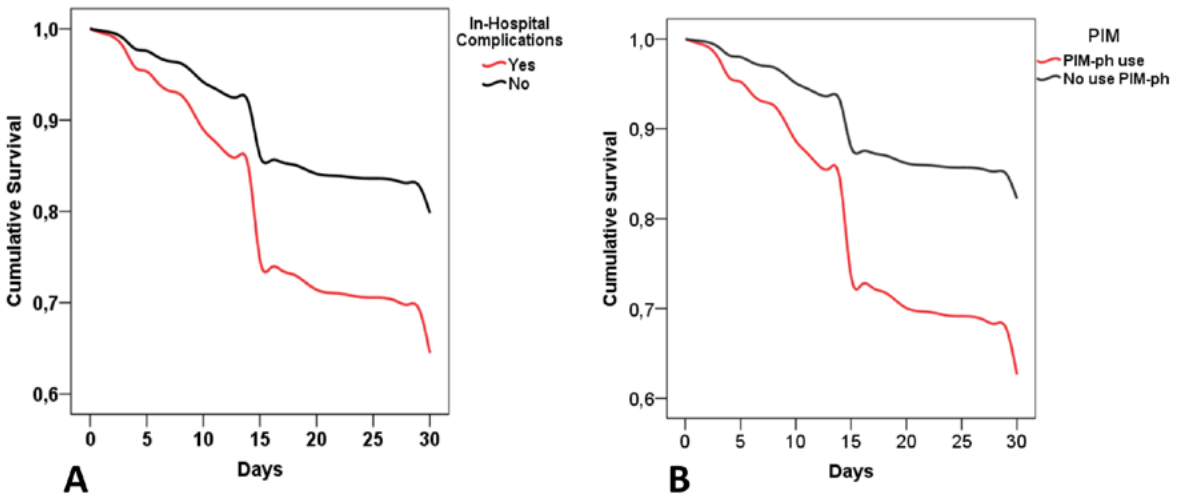

Figure 1. Cox regression survival analysis of potentially inappropriate medication used prior hospitalization (PIM-ph) of the older adults studied. (A) Comparison between older adults that presented in-hospital evolution of one or more of the following geriatric complications: delirium, immobility, urinary/fecal incontinence, and nosocomial infection) (*p≤0.001*); (B) with and without (controls) previous hospitalization use of potentially inappropriate medicines (PIM-ph). The cumulative survival was corrected by sex, age, frailty risk determined by the ISAR test, social support, confusion symptoms evaluated by the CAM test, and the in-hospital evolution of geriatric complications. The analysis of the curves observed the significance of $p<0,05$.

DISCUSSION

The present investigation observed that PIM-ph increased the mortality risk of older adults admitted in the emergency room at the University Hospital of the Federal University of Santa Maria (HUSM), Santa Maria, Rio Grande do Sul State, Brazil, up to 30 days after hospital discharge. This type of analysis has been little explored in previous studies, although it is well established that PIM use by older adults is a significant public health concern 5-6. Therefore, initially, it is relevant to comment that PIM-ph prevalence observed in the patients included in this study is similar to other investigations described in the literature [8,9,26].

Three specific PIM-ph were associated with a higher mortality risk: BDZ, digoxin, and loop diuretics. Among the PIMs associated with increased mortality, BDZ represents one of the most widely prescribed drugs in and out of hospital[27,28]. In pharmacological terms, BDZ effects involve an interaction with the central nervous system (CNS) mediated by the activation of GABA A receptors. Although a significant number of BDZs are approved by regulatory agencies, such as the Food Drug Administration (FDA) and *Agência Nacional de Vigilância Sanitaria* (ANVISA, Brazilian Health Ministry), these drugs have several side effects, including cognitive impairment, tolerance, rebound insomnia upon discontinuation, car accidents/falls, abuse, and dependence liability[29]. Moreover, BDZs can interact with other drugs, including sedatives, barbiturates, and ethanol, triggering respiratory depression owing to a synergistic effect[29]. BDZ can increase adverse effects in older patients due to age-related differences in pharmacokinetics and pharmacodynamics, leading to body BDZ accumulation and higher plasma concentrations[30]. Moreover, BDZ can cause physical dependence and withdrawal syndrome[27]. Therefore, the results described here suggest that, in addition to potential adverse effects, the use of BZP before hospitalization can impact the hospital outcome of older adult patients, increasing the risk of death.

Previous use of digoxin prescribed to treat cardiac conditions also increased mortality risk in the older adult investigated in this study. Cardiac glycosides, including digitalis and digoxin, have long been used in clinical practice. However, digoxin toxicity is clinically relevant as it can lead to fatal cardiac arrhythmias[28,31]. Some previous studies, such as those performed by Yang et al.[32] have described an association between digoxin use and mortality risk in patients with advanced chronic kidney disease. Results from a study that included 5.824 patients with atrial fibrillation (AF) taking digoxin showed an increased risk of death, regardless of heart failure[33]. The risk of digoxin intoxication in older adults with decreased kidney clearance is higher. The aging-associated pharmacological alterations could be the basis for explaining why the use of digoxin before hospitalization contributed to the increased mortality in the older adult investigated here.

Loop diuretics drugs were also identified as a PIM-ph capable of influencing the mortality rate of older adults. Loop diuretics are widely used to treat heart and renal failure, hypertension, and peripheral edema[33]. However, there are previous investigations, such as the study performed by Schartum-Hansen et al.[34], corroborating that loop diuretics could increase the risk of all-cause mortality in patients with suspected coronary artery disease.

Based on studies previously published in the literature, it is possible to infer that using some types of PIM-ph could increase mortality in hospitalized patients. However, studies with a design similar to the one described here are needed to identify to corroborate the relevance of identifying PIM used previously in the hospitalization of older adults. Another relevant limiting factor is the characteristics of hospital emergency, such as patient turnover and the absence of those responsible for information for the requested period.

CONCLUSION

The results described here show that the use of some types of potentially inappropriate drugs before hospitalization could represent a risk factor for mortality of older adults admitted from emergency rooms. These results represent a novelty, since in general the impact of this type of drug is evaluated when they are prescribed during hospitalization. In this context, the pharmacological management of elderly patients can be a factor that helps to prevent hospital complications and mortality.

AUTHORSHIP

- Thamara G. Flores - Conceptualization; Data curation; Formal analysis; Methodology ; Resources; Software; Supervision; Validation; Writing – original draft
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- Ana Cristina Gularte- Data curation; Methodology; Resources; Visualization; Writing – review & editing
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