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Potentially Inappropriate Prescriptions and Hospital Outcome among Geriatric Patients

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Background and aims. High risk medications use is common at hospitals and poses a major risk for frail older adults. The study aims to determine the association between Potentially Inappropriate Prescriptions (PIPs) and hospital outcome among geriatric patients.
Methods. A retrospective cohort study including 152 older adults (age ≥ 60 years). These patients were admitted to the intensive care unit (ICU) at Geriatrics hospital from August 1st, 2021 to January 1st, 2022. Age, sex, clinical data and medications used throughout admission were extracted for each patient. The target outcome was in-hospital mortality. PIPs were identified in accordance with Screening Tool of Older Persons' potentially inappropriate Prescriptions version 2 (STOPP v. 2). Logistic regression analysis was done to test the association between use of PIPs and in-hospital mortality. Descriptive statistics was performed for PIPs and medications use near the end of life.
Results. PIPs occurred in 67.8% (103 patients) of participants. Multivariate regression analysis revealed independent predictors of mortality including older age (OR = 1.075; 95% CI: 1.020-1.134; P .007), delirium/altered mental status on admission (OR = 2.688; 95% CI: 1.086-6.651; P .032), and utilizing of ≥ 3 PIPs (OR = 4.049; 95% CI: 1.320-12.421; P .014). Use of anticholinergics in patients with delirium or dementia was the most frequently reported PIPs among participants. **Conclusions.** PIPs are common and significantly associated with mortality among hospitalized older adults. The study provides an overview for high risk medications and recommends a structured medication reviews and de-prescribing practice for frail older adults.

Key words: anticholinergics, mortality, potentially inappropriate prescriptions, geriatric patients

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INTRODUCTION

The World Health Organization (WHO) has identified medication harm as a global priority and considered medication without harm as the third WHO global patient safety challenge [1]. Medication harm was defined as 'any negative patient outcome or injury, due to medication use' [2]. Geriatric patients are at a higher risk of drug related problems (DRPs) due to age-related changes in pharmacokinetics and pharmacodynamics besides polypharmacy and multimorbidity [3]. Polypharmacy among geriatric patients is a well-known risk factor for medication harm and DRPs [4]. High

alert medications are those with a high risk of causing significant harm if not used correctly, various lists have been proposed in clinical settings to assist clinicians in identifying and avoiding these medications, such as the list published by the Institute of Safe Medication Practices (ISMP) [5]. Beers criteria are one of the most widely used and specified tools to guide medication use in older adults [6]. Similarly, Screening Tool of Older Persons' Prescriptions (STOPP) is a comprehensive and reliable tool to identify PIPs among older adults [7]. STOPP v. 2 includes 80 clinical criteria to pick up PIPs in clinical sittings of geriatric patients [7]. This study aims to determine the association between PIPs and in-hospital mortality and to describe PIPs and medications use near end of life among geriatric patients.

PATIENTS AND METHODS

A retrospective cohort study including older adults (aged ≥ 60 years) who were admitted to ICU at Geriatrics hospital at Ain Shams University, Egypt from August 1st, 2021 to January 1st, 2022. Despite accepting the chronological age of ≥ 65 years as a definition of a geriatric person, the situation doesn't fit well in Africa including Egypt and it can be extended to the age of ≥ 60 years which is also the age of pension benefit [8], and the acceptable age for admission to the geriatrics hospital. The study included critically ill patients whose condition necessitated ICU admission, as these patients are the most vulnerable group of patients at the hospital and have the highest risk of utilizing PIPs with the occurrence of worse outcomes [9]. Exclusion criteria involved patients with missing medication sheets and/or outcome including those transferred to another hospital or those discharged against medical advice before completion of treatment regimen.

Review of medication sheets and administrative data records at geriatrics hospital was done by the principal investigator to extract demographics including age and sex and clinical data including co-morbidities and initial diagnosis. Medications use was confirmed by records of clinical pharmacist sheets at clinical pharmacy unit at Geriatrics hospital. PIPs were identified in accordance with STOPP v. 2 criteria [7].

Applicability of STOPP v. 2 criteria among participants was described in Supplementary materials, Table SI. The total number of PIPs for each patient was calculated and patients were grouped accordingly. Target outcome was in-hospital mortality, based on the documented clinical status at the time of hospital discharge either death or discharge alive. Medications with anticholinergic properties were detected with assistance of anticholinergic list [10] and their total number was calculated for each patient. Because of the variability in the anticholinergic properties of different agents ranging from low to high anticholinergic effects, the cumulative anticholinergic burden (ACB) was estimated utilizing ACB calculator to estimate the total anticholinergic load for patients utilizing more than one agent with anticholinergic side effects [11].

Statistical analysis

Values were presented as numbers and proportions or mean and standard deviation. The distribution of qualitative variables among patient groups were compared by Chi-square test or Fisher's exact test, as indicated. Quantitative variables were checked for normality by Shapiro-Wilk test. As data were normally distributed, variables were compared between groups by independent t-test. Individual drugs with P values < 0.05 in univariate analysis were introduced in a logistic regression model to detect independent predictors of mortality. All tests were bilateral and a P value of 5% is the limit of statistical significance. Analysis was performed by statistical package software IBM-SPSS version 24.

RESULTS

A total of 152 geriatric patients were included. In-hospital mortality occurred in 101 (66.4%) patients with mean age of 76.9 ± 8.5 years. Participant's characteristics were compared between the alive and dead group. Significant variables were age, delirium/altered mental status on admission, using PIPs-STOPP v. 2, number of PIPs per patient, use of ≥ 3 PIPs, using medications with anticholinergic properties and the number of anticholinergics per patient. The same was found when the variables were measured as odds ratio. A one-year increase in age would increase the odds of mortality by 1.0. By 95%, the one-year increase in age would increase the odds of mortality from 1.0 to 1.1. Using PIPs-STOPP would increase the odds by 5.3. By 95%, using PIPs-STOPP would increase the odds of mortality from 2.5 -11.1. With each additional PIPs-STOPP utilized the odds would increase by 1.9 times and with each additional anticholinergic medication utilized the odds would increase by 1.7 times (Tab. I).

As numeric variables of PIPs-STOPP and anticholinergics did not fit the regression model, the following variables were entered into multivariate regression analysis: age, delirium/altered mental status on admission, use of PIPs-STOPP, use of ≥ 3 PIPs and use of anticholinergics. Significant predictors of mortality were age (OR = 1.075; 95% CI: 1.020-1.134; P. 007), presence of delirium/altered mental status on admission (OR = 2.688; 95% CI: 1.086-6.651; P. 032), and the use of ≥ 3 PIPs (OR = 4.049; 95% CI: 1.320-12.421;

Table I. Association between Socio-demographic/clinical characteristics and in-hospital mortality.

Socio-demograghic/clinical characteristics	Alive n = 51 (33.6%)	Dead n = 101 (66.4%)	P value	Univariate logistic regression	
				OR 95% CI	P value
Age Mean ± SD	72.2 ± 7.8	76.9 ± 8.5	**.002**	1.073 (1.025-1.123)	**.002**
Male/female	23 (38.3%)/28 (30.4%)	37 (61.7%)/64 (69.6%)	.313	.704 (.355-1.395)	.314
Delirium/altered mental status on admission	15 (18.1%)	68 (81.9%)	**< .001**	4.945 (2.379-10.282)	**< .001**
PIPs-STOPP v.2	22 (21.4%)	81 (78.6%)	**< .001**	5.339 (2.549-11.182)	**<. 001**
Number of PIPs-STOPP v. 2 per patient	.9 ± 1.3	2.7 ± 1.9	**< .001**	1.919 (1.484-2.483)	**<. 001**
1 PIP	10 (47.6%)	11 (52.4%)	.141	.501 (.197-1.273)	.146
2 PIPs	5 (29.4%)	12 (70.6%)	.701	1.240 (.412-3.735)	.702
≥ 3 PIPs	7 (10.6%)	59 (89.4%)	**< .001**	8.830 (3.625-21.509)	**< .001**
Anticholinergics	36 (29.3%)	87 (70.7%)	**.021**	2.589 (1.134-5.911)	**.024**
Number of anticholinergics per patient	1.3 ± 1.1	2.5 ± 1.6	**< .001**	1.747 (1.335-2.285)	**< .001**
Cardiac disease	15(24.2%)	47(75.8%)	.310	1.495 (.686-3.262)	.312
Diabetes mellitus	11 (20.8%)	42 (79.2%)	.108	1.948 (.858-4.424)	.111
Old stroke/Transient ischaemic attack	6 (24.0)	19 (76.0)	.591	1.319 (.480 -3.629)	.591
Chronic kidney disease	5 (16.1)	26 (83.9)	.088	2.442 (.856-6.965)	.095
Chronic liver disease	7 (24.1)	22 (75.9)	.587	1.302 (.501-3.381)	.588
Malignant disease	4 (16.0)	21 (84.0)	.120	2.435 (.772-7.678)	.129
Dementia	6 (35.3)	11 (64.7)	.565	.688 (.234-2.024)	.496
Chronic respiratory disease	6 (31.6)	13 (68.4)	.717	.823 (.287-2.362)	.717
Hypertension	19 (26.8)	52 (73.2)	.655	1.193(.550-2.589)	.655
Thyroid disease	2 (33.3)	4 (66.7)	1.000	.782(.137-4.467)	.782

P .014). The model was able to explain 35.6% of the variability of mortality as indicated by Nagelkerke R Square value. It was able to correctly predict mortality by 80.1%. The results showed that taking ≥ 3 PIPs, the odds of mortality would increase by 4 times. With older age, the odds of mortality would increase by 1 time. Also, presence of delerium/altered mental status on admission would increase the odds of mortality by 2.7 times. The 95 CI means that by 95% we are confident that taking ≥ 3 PIPs would increase the odds of mortality from 1.3 to 12.4 times. While, an increase in age with one year would increase the mortality odds from 1.0 to 1.1 times. Also, presence of delirium/altered mental status on admission may increase the odds of mortality between 1.0-6.6 times as described in (Tab. II).

The distribution of PIPs-STOPP and anticholinergics are described in (Tabs. III-IV). Medications use near end of life and distribution of cardiovascular system (CVS) and central nervous system (CNS) acting medications are also described in (Figs. I-II). Apart of antibiotics, ranking of individual medication use near end of life including the top 10 commonly prescribed medications was performed; Omeprazole (9.4%), followed by dobutamine/noradrenaline/epinephrine (6.3%) and salbutamol/ipratropium/budesonide (5.9%) were the most frequently prescribed medications (Supplementary materials, Table SII).

DISCUSSION

Life expectancy in Egypt increased to 74.3 years and the total number of geriatric population reached 6.8 millions, representing 6.7% of the total population in 2021 with

Table II. Multivariate regression analysis of significant variables.

Significant variables	Multivariate logistic regression	
	OR 95% CI	P value
Age	1.075 (1.020-1.134)	**.007**
Delirium/altered mental status on admission	2.688 (1.086-6.651)	**.032**
PIPs-STOPP v. 2	1.726 (.601-4.959)	.310
≥ 3 PIPs	4.049 (1.320-12.421)	**.014**
Anticholinergics	.982 (.328-2.941)	.974

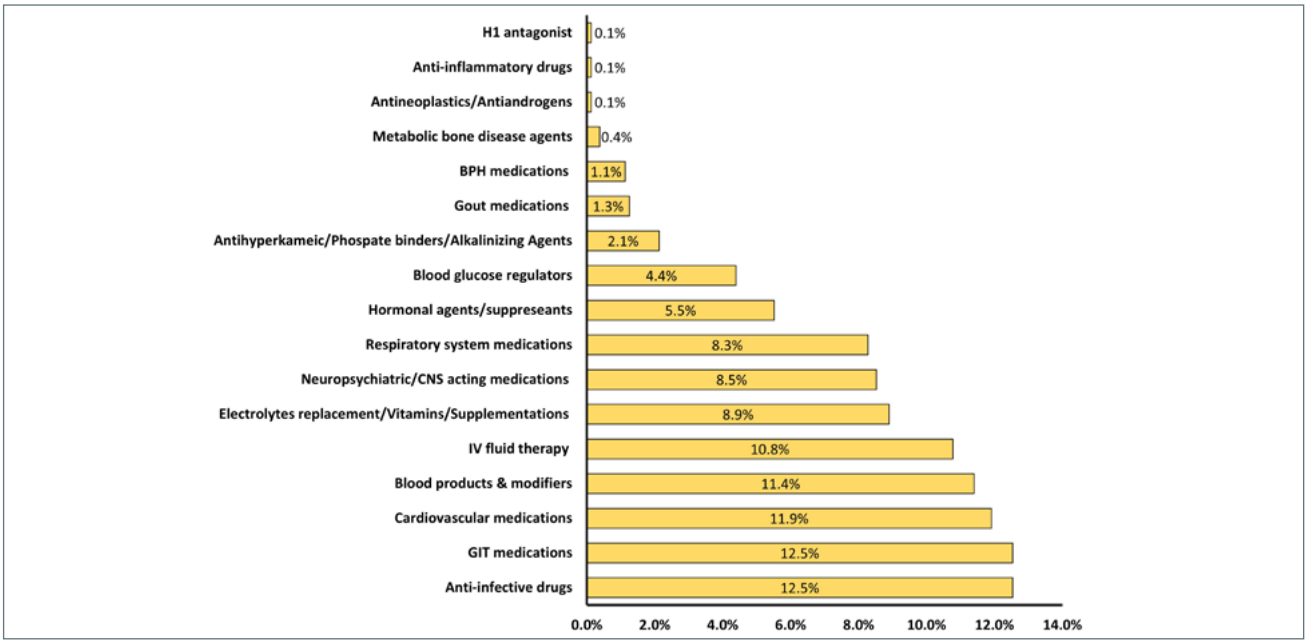

Figure 1. Description of medications use near end of life: main categories of medications.

subsequent higher health care utilization and costs [12]. The study included critically ill geriatric patients, because of the higher risk of utilizing PIPs with subsequent occurrence of DRPs and in-hospital mortality [8]. PIPs occurred in (103 patients) 67.8% of participants. The increasing number of PIPs was associated with increased risk of death at hospital. This study utilized STOPP v. 2 criteria [7] to identify PIPs among hospitalized older patients and showed that using of ≥ 3 PIPs was a significant predictor of in-hospital mortality. This finding manifests the clinical impact of utilizing PIPs at acute care sittings on hospital outcome and it correlates with a previous study showed that utilizing ≥ 1 PIPs was associated with an increased risk of mortality at a longer term of 36-months' follow-up [13]. Similarly, another cohort study among community dewelling older adults in Bambuí, Brazil showed that PIPs, according to Beers criteria was a predictor of mortality with a significant association between the number of PIPs and risk of death [14].

The association between in-hospital mortality and every other socio-demographic and clinical variable was assessed by logistic regression analysis. Older age was also a significant predictor of mortality that could be attributed to higher prevalence of frailty in older age group [15].

Besides using of ≥ 3 PIPs and older age as significant predictors of mortality, the current study explored the prognostic effect of delirium/altered mental status on hospital admission. In the current study, 54.6% (83 patients) had delirium/altered mental status on admission. Delirium is a common condition among hospitalized geriatric patients and associated with poor outcomes [13]. It necessitates a vigilant screening for its presence at the time of admission to provide the appropriate management and early non-pharmacologic interventions [16]. Based on the application of STOPP v. 2 criteria on the prescribed medications, study results reported the most frequently encountered PIPs to avoid as follows:

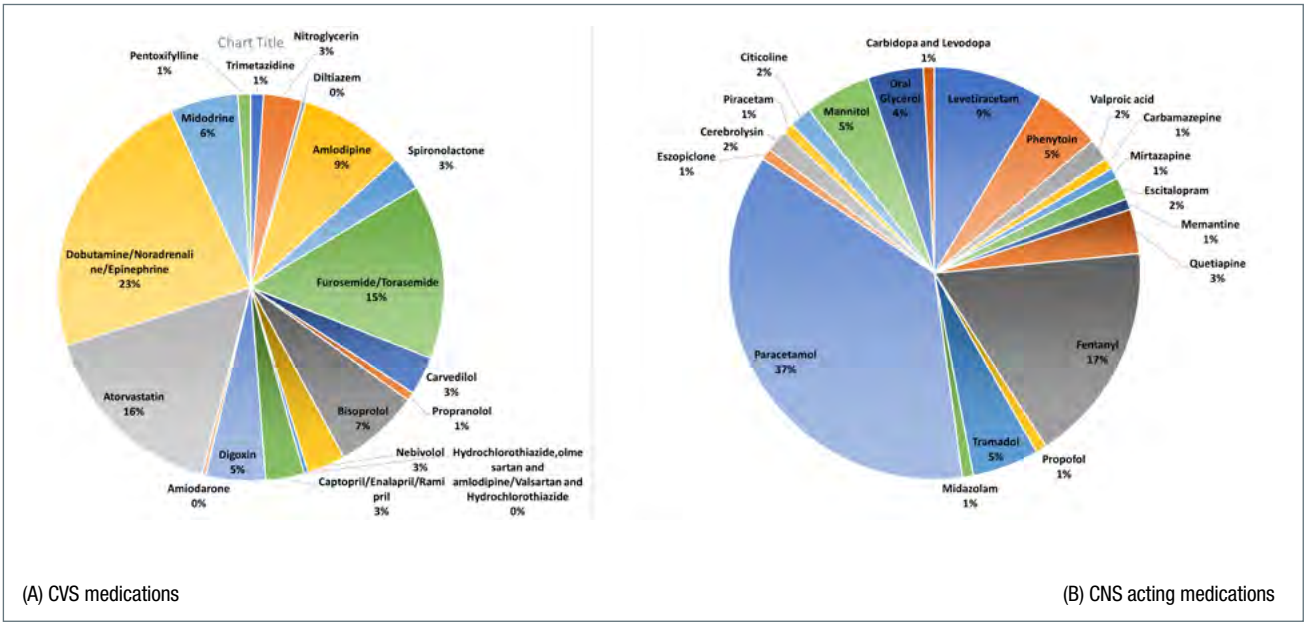

Figure 2. Description of medications use near end of life.

anticholinergics/antimuscarinics use in patients with delirium or dementia (82 cases), use of regular opioids without concomitant laxative (21 cases), drugs likely to cause constipation such as aluminum antacids or anticholinergics in patients with chronic constipation (15 cases), aspirin plus clopidogrel as secondary prevention of stoke (13 cases), concurrent use of antiplatelets with a new oral anticoagulant (NOAC) (9 cases), aldosterone antagonists with concurrent use of angiotensin-converting enzyme (ACE) inhibitors (9 cases), and use of neuroleptics (8 cases). The study supports the special considerations that should be taken during prescribing for older adults including the high concerns about the presence of geriatric syndromes, reduced creatinine clearance and presence of Electrocardiogram (ECG) abnormalities such as QT prolongation. It is evidenced by the presence of several PIPs including the use of diuretics with concurrent urinary incontinence, Factor Xa inhibitors with an estimated glomerular filtration rate (eGFR) < 15 ml/min/1.73m^2, and escitalopram with other drugs inducing QT prolongation. Geriatric syndromes such as delirium, dementia, falls, and urinary incontinence are common and render geriatric patients at high risk of poor quality of life, situational challenges and even death [17].

The current study highlights the prognostic value of utilizing medications with anticholinergic properties, as these medications could be associated with higher risk of delirium and in-hospital mortality in frail older adults [18]. Another longitudinal study showed a dose-dependent association between anticholinergics use and the risk of cerebrovascular accidents and mortality in geriatric patients with dementia [19].

Our study showed that increasing number of anticholinergics was significantly associated with in-hospital mortality. There is a long list of drugs defined as having anticholinergic properties, many of these drugs are essential for some cases and cannot be easily stopped or substituted with subsequent risk of adverse drug effects and delirium [18,20]. The most commonly encountered medications with anticholinergic properties in this study included the following: Ipratropium (67 cases), Furosemide (49), Hydrocortisone/Methylprednisolone/Prednisolone (34), Piperacillin (33), Fentanyl (20) and Digoxin (16). The study also highlights the link between the aging brain, delirium/dementia and PIPs including anticholinergics. The study showed that only 12 (14.6%) out of 82 patients who utilized anticholinergic agents in the presence of delirium or dementia survived to discharge from the hospital. It coincides with previous studies showing the association between anicholinergics use and mortality in the presence of delirium [21] and especially in the presence of underling cognitive impairment [22]. Because of these possible deleterious effects of anticholinergic agents in older adults, cost-benefit assessment and de-prescribing practice could markedly improve patient outcomes [23].

On the other side, the study described medications use near the end of life. A previous expert panel have reached consensus on 10 medication classes described as “often inadequate” for continuation during the last 3 months of life such as lipid-lowering agents,

Table III. Potentially inappropriate prescriptions-STOPP Criteria v. 2.

PIPs-STOPP criteria v.2	Total NO.	Alive n = 51 (33.6%)	Dead n = 101 66.4%
Digoxin for heart failure with preserved ejection fraction	3	0 (0.0%)	3 (100.0%)
Absence of an evidence-based clinical indication	2	0 (0.0%)	2 (100.0)
Diuretics with concurrent urinary incontinence	1	0 (0.0%)	1 (100.0%)
Hypnotic Z-drugs	1	0 (0.0%)	1 (100.0%)
Alpha-1 receptor blockers with the presence of hypotension	1	0 (0.0%)	1 (100.0%)
Centrally-acting antihypertensives e.g methyldopa	1	1 (100.0%)	0 (0.0%)
Neuroleptics	8	4 (50.0%)	4 (50.0%)
Anticholinergic Burden Score ≥ 4	3	2 (66.7%)	1 (33.3%)
Amiodarone	1	0 (0.0%)	1 (100.0%)
Non-selective Beta blockers with uncontrolled heart failure	1	0 (0.0%)	1 (100.0%)
Factor Xa inhibitors with GFR < 15 ml/min/1.73m^2	2	0 (0.0%)	2 (100.0%)
Use of NSAIDs with warfarin	1	0 (0.0%)	1 (100.0%)
Aspirin plus clopidogrel as secondary stroke prevention	13	5 (38.5%)	8 (61.5%)
Oral elemental iron doses greater than 200 mg daily	4	0 (0.0%)	4 (100.0%)
Acetylcholinesterase inhibitors with concurrent treatment with drugs that reduce heart rate such as digoxin	1	0 (0.0%)	1 (100.0%)
Drugs likely to cause constipation (e.g. anticholinergic drugs, aluminum antacids) in patients with chronic constipation	15	1 (6.7%)	14 (93.3%)
Antiplatelets plus new oral anticoagulant	9	2 (22.2%)	7 (77.8%)
Ipratropium in the presence of benign prostatic hyperplasia	3	0 (0.0%)	3 (100.0%)
Anticholinergics in patients with delirium or dementia	82	12 (14.6%)	70 (85.4%)
ACEIs with concurrent use of Angiotensin receptor blockers (ARBs)	1	1 (100.0%)	0 (0.0%)
Aldosterone antagonists with concurrent use of ACEIs	9	5 (55.6%)	4 (44.4%)
Theophylline	1	1 (100.0%)	0 (0.0%)
Use of regular opioids without concomitant laxative	21	0 (0.0%)	21 (100.0%)
Escitalopram with other drugs inducing QT prolongation	3	1 (33.3%)	2 (66.7%)

anti-dementia and osteoporosis drugs but it remained unaccomplished for others such as proton pump inhibitors, haloperidol, furosemide and selective serotonin reuptake inhibitors [24].

In this study, the most commonly utilized medication classes among the dead group included anti-infectives (12.5%) and GIT medications (12.5%), followed by CVS medications (11.9%). Medications use in terminally ill patients should be guided by a specified and patient-centered criterion such as STOPPFrail version 2 which is a promising tool for geriatric patients near end of life and includes a list of medication classes that may be inappropriate and have minimal or no benefits for frail and terminally ill older patients [25]. This tool is mainly recommended for older patients with limited life expectancy for whom the target of management is to reduce DRPs and improve quality of life, these patients should have all of the following: functional dependency and/or severe chronic disorder and/or terminal condition, presence of irreversible frailty, poor outcome regarding 1-year survival [25]. Our study did not include frailty assessment and involved critically ill patients who wouldn't necessarily fullfil all the previously mentioned criteria. Accordingly, applying STOPP v. 2 criteria was more convenient for our analysis.

In this study, individual drug ranking among the dead group of patients was performed as described in the results section. The most frequently prescribed medications near end of life were; omeprazole (9.4%), dobutamine/noradrenaline/epinephrine (6.3%) and salbutamol/ipratropium/budesonide (5.9%). For the clinical significance, we analyzed CNS acting medications

Table IV. Medications with anticholinergic properties.

Medications with anticholinergic properties	Total Number	Alive n = 51 (33.6%)	Dead n = 101 (66.4%)
Warfarin	1	0 (0.0%)	1 (100.0%)
Famotidine	4	0 (0.0%)	4 (100.0)
Domperidone	1	0 (0.0%)	1 (100.0%)
Diltiazem	1	0 (0.0%)	2 (100.0%)
Digoxin	16	2 (12.5%)	14 (87.5%)
Theophylline	1	1 (100.0%)	0 (0.0%)
Valproic acid	3	1 (33.3%)	2 (66.7%)
Carbamazepine	3	2 (66.7%)	1 (33.3%)
Mirtazapine	2	1 (50.0%)	1 (50.0%)
Escitalopram	3	1 (33.3%)	2 (66.7%)
Quetiapine	8	4 (50.0%)	4 (50.0%)
Fentanyl	20	0 (0.0%)	20 (100.0%)
Tramadol	7	1 (14.3%)	6 (85.7%)
Midazolam	1	0 (0.0%)	1 (100.0%)
Carbidopa and levodopa	1	0 (0.0%)	1 (100.0%)
Metformin	1	1 (100.0%)	0 (0.0%)
Atropine	2	2 (100.0%)	0 (0.0%)
Colchicine	3	3 (100.0%)	0 (0.0%)
Captopril	17	10 (58.8%)	7 (41.2%)
Furosemide	49	9 (18.4%)	40 (81.6%)
Hydrocortisone/methylprednisolone/ prednisolone	34	8 (23.5%)	26 (76.5%)
Ipratropium	67	12 (17.9%)	55 (82.1%)
Cetirizine	2	1 (50.0%)	1 (50.0%)
Piperacillin	33	4 (12.1%)	29 (87.9%)
Clindamycin	8	2 (25.0%)	6 (75.0%)
Gentamycin	2	0 (0.0%)	2 (100.0%)
Ampicilin	9	2 (22.2%)	7 (77.8%)
Vancomycin	3	2 (8.0%	23 (92.0%)

and showed the most commonly utilized medications: paracetamol (37%), followed by fentanyl (17%) and levetiracetam (9%). On the other side, analysis of CVS medications included dobutamine/noradrenaline/epinephrine (23%), followed by atorvastatin (16%) and furosemide/torsemide (15%). These data contradict previous studies reporting morphine, midazolam and haloperidol as the most frequently prescribed drugs near the end of life in one of the largest palliative care centers in the Netherlands [26]. This difference in the patterns of medication use near the end of life could be attributed to the heterogeneity of the studied population and clinical sittings in various studies. The current study included ICU patients with relatively younger age. Also, it is worth reporting that omeprazole, atorvastatin and aspirin were among the top 10 prescribed medications among participants near end of life despite of the presence of these medications in STOPPFrail version 2 list [25]. This conflict might also be related to ICU sitting, presence of a situational clinical necessity, and the "younger" cut-off for defining the geriatric patients in the study. These findings support shared decision making, reasonable justification of medication use and de-prescribing practice to reduce DRPs among frail older patients [25].

STRENGTHS AND LIMITATIONS

To the best of our knowledge, this is the first study assessing the association of PIPs in accordance with STOPP v. 2 criteria and mortality among critically ill older adults with description of a thorough overview of both PIPs and medication use near of life. The major limitation of the study is the non-applicability of certain items in STOPP v. 2 criteria with possible over- or underestimation of PIPs use. It is attributed to the retrospective design and lack of some information regarding physical examination, laboratory results and pre-hospitalization medication history. Similar limitations related to applying different explicit criteria have been reported in various studies [27,28].

The small sample size at a single institute and the missing assessment of potential confounders of mortality such as acute illness severity and functional/frailty status are additional limitations of the study. Further exploration of the interplay between PIPs, frailty status and mortality among older adults in different health care settings is needed.

CONCLUSIONS

PIPs are common and frequently associated with worse outcomes in hospitalized older adults. Meticulous medication selection is crucial and requires an evidence-based approach to detect and avoid high-risk medications. It includes structured medication reviews and de-prescribing practices to improve clinical outcomes and avoid futile management in acute care settings of geriatric patients. Also, the provision of novel, easily applicable tools and pop-up alerts in software to detect PIPs among frail older adults is of paramount importance in the meantime.

Ethical consideration

The study protocol was revised and approved by Research Ethics Committee at Geriatrics hospital and Research Ethics Committee of the faculty of Medicine at Ain Shams University, Approval code: FMASU R 56/2022.

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Conflict of interest

The Authors declare no conflict of interest.

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Author contributions

All Authors have contributed to the study through data analysis and manuscript writing. Khalid E. Elsorady has also contributed to the study design/concept, data collection/entry and manuscript drafting. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIALS

Table SI. Applicability of STOPP v. 2 criteria among the studied sample.

STOPP criteria	Applicability
Cardiovascular system	
Beta-blocker in the presence of heart block/bradycardia or in combination with with diltiazem or verapamil	Applicable through review of medication charts and comorbidities
Thiazide diuretic in the presence of gout or current electrolyte disturbance including hyponatremia, hypokalaemia and hypercalcaemia	Based on the documented history and electrolytes disturbances, but serum levels of these electrolytes couldn't be determined
Centrally-acting antihypertensives such as methyldopa unless evident intolerance or absence of efficacy with other classes of antihypertensives	Applicable through review of medication charts, but intolerance to other antihypertensives couldn't be determined
Amiodarone as first-choice medication for supraventricular tachyarrhythmias	Applicable through review of medication charts and absence of other antiarrhythmics
Digoxin for heart failure with preserved ejection fraction	Applicable through review of medication charts and comorbidities
Loop diuretic for dependent ankle swelling without evidence of hepatic failure, cardiac failure, kidney failure or nephrotic syndrome	Not applicable as dependent ankle oedema couldn't be determined
Loop diuretic as first-choice medication for hypertension	Applicable through review of medication charts and comorbidities
Aldosterone antagonists as spironolactone and eplerenone with concurrent potassium-preserving medications as ACEI's and ARBs without a regular follow up of serum potassium	Applicable through review of medication charts, but monitoring of serum potassium couldn't be determined
Diltiazem or Verapamil with NYHA Class III or IV cardiac failure	Admission due to acute cardiac failure on top of congestive heart failure or cardiogenic shock indicates severe heart failure
Phosphodiesterase type-5 inhibitors as sildenafil in severe cardiac failure or concurrent nitrate use for angina due to the risk of circulatory collapse	Applicable through review of medication charts
Loop diuretic for treatment hypertension in the presence of urinary incontinence	Applicable through review of medication charts and the documented history of urinary incontinence
ACEIs or ARBs in patients with elevated serum potassium	Applicable through review of medication charts and documented electrolyte disturbances
Central nervous system	
Neuroleptics with moderate-high anticholinergic properties such as chlorpromazine and clozapine with a history of prostatism or previous urinary retention	Applicable through review of medication charts and the presence of BPH
Citalopram and Escitalopram with concomitant QT interval prolongation or concurrent medications that induce QT interval prolongation in Electrocardiogram (ECG)	Applicable through review of medication charts i.e concurrent use of Escitalopram with levofluxacin, but QT prolongation in ECG couldn't be determined
Acetylcholinesterase inhibitors in the presence of a history of heart block or recurrent unexplained syncope or persistent bradycardia or with concurrent use of medications that induce bradycardia such as beta-blockers, digoxin and diltiazem	Applicable through review of medication charts and medical history
Tricyclic antidepressants in the presence of dementia, cardiac conduction abnormalities, narrow angle glaucoma, prostatism, or prior urinary retention	Applicable through review of medication charts and comorbidities
Tricyclic antidepressants as first-choice antidepressant medications	Prescribing of TCA in the absence of SSRIs or SNRIs
Anticholinergics/antimuscarinics in patients with dementia or delirium	Applicable through review of medication charts and medical history
Neuroleptic antipsychotic in dementia associated with psychological and behavioural manifestations unless symptoms are marked and resistant to non-pharmacological interventions	Applicable through review of medication charts and medical history but severity of psychotic symptoms and failure of non-pharmacologic treatments couldn't be determined

Table SI. Applicability of STOPP v. 2 criteria among the studied sample.

STOPP criteria	Applicability
Dopamine agonists or levodopa for treatment of benign essential tremor	Applicable through review of medication charts and medical history
First-generation antihistamines	Applicable through review of medication charts
Phenothiazines as first-choice medications, with the exception of levomepromazine for vomiting in palliative sittings, chlorpromazine for persistent hiccoughs and prochlorperazine for nausea, vomiting and vertigo	Applicable through review of medication charts
Neuroleptics for hypnosis, unless sleep problem is due to dementia or psychosis	Applicable through review of medication charts and medical history
Anticholinergics/antimuscarinics for extra-pyramidal adverse effects of neuroleptic agents	Applicable through review of medication charts, but extrapyramidal symptoms couldn't be determined
SSRI's with significant hyponatraemia (serum Na+ < 130 mmol/l)	Applicable through review of medication charts and documented electrolyte disturbances
Benzodiazepines (BZDs) for ≥ 4 weeks duration. Abrupt withdrawal for all BZDs should be avoided if taken for > 4 weeks	Applicable through review of duration of medication intake on charts
Antipsychotics with the exception of quetiapine or clozapine in the presence of Lewy Body disease or Parkinsonism	Applicable through review of medication charts and the presence of parkinsonism or Lewy Body disease
Gastrointestinal system	
Oral elemental iron doses > 200 mg/day (ferrous gluconate > 1800 mg/day,ferrous fumarate > 600 mg/day, ferrous sulphate > 600 mg/day)	Applicable through review of iron doses in medication charts
Medications likely to reduce bowel motions such as anticholinergics, aluminium antacids, opioids, oral iron and verapamil in the presence of chronic constipation	Applicable through review of iron doses in medication charts. Co-existing prescribing of laxatives indices constipation
Prochlorperazine or metoclopramide in the presence of Parkinsonism	Applicable through review of medication charts and comorbidities
Proton Pump inhibitors (PPI) for erosive oesophagitis or uncomplicated peptic ulcer at full therapeutic dose for > 8 weeks	Applicable through review of duration of medication intake in charts, but pre-admission intake of PPI couldn't be determined
Respiratory system	
BZDs in the presence of acute or chronic respiratory failure ($pO2 < 8.0$ kPa ± $pCO2 > 6.5$ kPa)	Applicable through review medication charts and comorbidities/cause of admission
Bronchodilators with anti-muscarinic properties such as ipratropium and tiotropium in the presence of bladder outflow obstruction or narrow angle glaucoma	Applicable through review medication charts and presence of either glaucoma or BPH/bladder outlet obstruction in comorbidities
Theophylline as monotherapy for chronic obstructive pulmonary disease (COPD)	Applicable through review medication charts with absence of other treatment options for COPD
Systemic corticosteroids instead of inhaled corticosteroids for maintenance treatment in moderate and severe COPD	Applicable through review medication charts and comorbidities
Musculoskeletal system	
COX-2 selective Non-steroidal anti-inflammatory drug (NSAIDs) in the presence of cardiovascular disease	Applicable through review of medication charts and comorbidities
NSAID with concomitant use of corticosteroids without PPI prophylaxis	Applicable through review of medication charts
Oral bisphosphonates in the presence of upper gastrointestinal disease (GIT),upper GIT bleeding or peptic ulcer disease	Applicable through review of medication charts and comorbidities
NSAID with severe hypertension or severe cardiac failure	Presence of hypertensive urgency or emergency on admission indicates severe hypertension
Quinine if no benefit after 4 weeks, take a drug holiday every 3 months	Not applicable as duration of quinine Intake before admission couldn't be determined
NSAID other than COX-2 selective medications in the presence of GIT bleeding or peptic ulcer disease, unless with coexisting use of PPI or H2 blocker	Applicable through review medication charts and comorbidities

Table SI. Applicability of STOPP v. 2 criteria among the studied sample.

STOPP criteria	Applicability
NSAID for > 3 months for osteoarthritis pain without a trial of paracetamol use	Applicable through review of duration of medication intake on charts, but pre-admission intake of NSAIDs couldn't be determined
Corticosteroids use for > 3 months as monotherapy for rheumatoid arthrtitis	Applicable through review medication charts and comorbidities
Corticosteroids for osteoarthritis (except for periodic mono-articular injection for pain management)	Applicable through review medication charts and comorbidities
Colchicine or NSAID use for > 3 months for gout in the absence of a contraindication to a xanthine-oxidase inhibitor	Prescribing of NSAIDs or colchicine and recorded rheumatoid arthritis indicates therapy > 3 months
Urogenital system	
Selective alpha-1 blockers in the presence of micturition syncope or orthostatic hypotension	Applicable through review of medication charts and comorbidities, but postural hypotension couldn't be determined
Anticholinergics/antimuscarinics in the presence of dementia or narrow-angle glaucoma or prostatism	Applicable through review of medication charts and comorbidities
Medications that increase urinary flow including diuretics in the presence of urinary incontinence	Applicable through review of medication charts and comorbidities
Endocrine system	
Oestrogens with a coexisting history of venous thromboembolism or breast cancer	Applicable through review of medication charts and comorbidities
Oestrogens without added progestogen in patients with intact uterus	Applicable through review of medication charts and comorbidities
Androgens without primary or secondary hypogonadism	Applicable through review of medication charts and comorbidities
Beta-blockers in the presence of diabetes mellitus (DM) with recurrent episodes of hypoglycaemia	Applicable through review of medication charts and recorded history of hypoglycaemia
Denosumab or bisphosphonates with low risk of fracture based on FRAX assessment tool	Applicable through review of medication charts, but FRAX couldn't be determined
Denosumab use in the absence of regular dental follow-up	Applicable through review of medication charts, but dental check-up couldn't be determined
Oral bisphosphonates in the presence of unexplained thigh, groin pain or upper GIT bleeding, or > 5 years after discussing benefits and risks	Applicable through review of medication charts and comorbidities, but duration of its intake couldn't be determined
Long acting sulphonylureas such as glimepiride, and glibenclamide for type 2 DM	Applicable through review of medication charts and comorbidities
Thiazolidenediones such as pioglitazone and rosiglitazone in the presence of cardiac failure	Applicable through review of medication charts and comorbidities
Drugs that predictably increase the risk of falls in older people	
Neuroleptics (related to extra-pyramidal side effect and gait dyspraxia)	Applicable through review of medication charts and comorbidities
Hypnotic Z-drugs such as zopiclone, zaleplon, and zolpidem (related to ataxia and daytime sedation)	Applicable through review of medication charts and comorbidities
Vasodilator drugs such as ACE inhibitors, ARBs, calcium channel blockers, alpha-1 receptor blockers and long-acting nitrates in the presence of postural hypotension	Applicable through review of medication charts and comorbidities, but postural hypotension couldn't be determined
BZDs (related to sedation,diminished sensorium and impaired balance)	Applicable through review of medication charts and comorbidities
Analgesic drugs	
Use of regular opioids without concurrent laxative	Applicable through review of medication charts

Table SI. Applicability of STOPP v. 2 criteria among the studied sample.

STOPP criteria	Applicability
Use of strong opioids such as fentanyl, tramadol and morphine as first-choice treatment for mild pain regardless of WHO analgesic ladder	Not applicable as as opioids frequently utilized for sedation on mechanical ventilation at intensive care unit. Also pain assessment is lacking
Long-acting opioids for break-through pain (without short-acting opioids)	Not applicable as opioids frequently utilized for sedation on mechanical ventilation at intensive care unit. Also pain assessment is lacking
Indication of medication	
Any medication prescribed for a longer course of therapy than its recommended duration	Applicable through review of medication charts
Any duplicate medication class prescription before optimizing monotherapy within a single medication class	Applicable through review of medication charts
Any medication prescribed without a clear indication according to the evidence-based practice	Applicable through review of medication charts and co-morbidities
Renal system	
Direct thrombin inhibitors (DTIs) such as dabigatran with an estimated glomerular filtration rate (eGFR) < 30 ml/ min/1.73 m^2	Applicable through review of medication charts and presence of either End Stage Renal Disease (ESRD) or Acute Kidney Injury (AKI) as GFR couldn't be determined
Factor Xa inhibitors such as rivaroxaban and apixaban with eGFR < 15 ml/ min/1.73 m^2	Applicable through review of medication charts and presence of either ESRD or AKI as GFR couldn't be determined
Metformin with eGFR < 30 ml/min/1.73m^2	Applicable through review of medication charts and presence of either ESRD or AKI as GFR couldn't be determined
Digoxin for a long-term use in a dose >125 µg/day with eGFR < 30 ml/ min/1.73 m^2	Applicable through review of medication charts and presence of either ESRD or AKI as GFR couldn't be determined
Colchicine with eGFR < 10 ml/min/1.73 m^2	Applicable through review of medication charts and presence of either ESRD or AKI as GFR couldn't be determined
NSAID's with eGFR < 50 ml/min/1.73 m^2	Applicable through review of medication charts and presence of either ESRD or AKI as GFR couldn't be determined
Anticoagulants/antiplatelets	
Aspirin with a previous history of peptic ulcer disease without coexisting PPI use	Applicable through review of medication charts and comorbidities
Aspirin plus clopidogrel as a secondary prevention of stroke (except if coexisting significant carotid arterial stenosis, acute coronary syndrome or coronary stenting within the last 12 months.	Applicable through review of medication charts and comorbidities
Vitamin K antagonist, DTI, or factor Xa inhibitors for first deep venous thrombosis without persistence of the provoking factors (e.g. thrombophilia) for > 6 months	Applicable through review of medication charts and comorbidities
Vitamin K antagonists, aspirin, clopidogrel, dipyridamole, DTIs or factor Xa inhibitors in the presence of high risk of bleeding such as uncontrolled severe hypertension and bleeding tendency	Applicable through review of medication charts and comorbidities
Factor Xa inhibitors, vitamin K antagonist or DTI for first pulmonary embolism without persistence of the provoking factors (e.g. thrombophilia) for > 12 months	Applicable through review of medication charts and comorbidities
NSAID, vitamin K antagonist, DTI or factor Xa inhibitors in combination	Applicable through review of medication charts
Aspirin combined with vitamin K antagonist, DTI or factor Xa inhibitors in patients with chronic atrial fibrillation	Applicable through review of medication charts and comorbidities

Table SI. Applicability of STOPP v. 2 criteria among the studied sample.

STOPP criteria	Applicability
Aspirin at doses > 160 mg/day for a long-term	Not applicable as pre-admission dose of aspirin couldn't be determined
Ticlopidine at any situation as prasugrel and clopidogrel are more convenient alternatives	Applicable through review of medication charts
Antiplatelet medications combined with vitamin K antagonist, DTI or factor Xa inhibitors in patients with cerebrovascular, stable coronary, or peripheral arterial disease	Applicable through review of medication charts and comorbidities
NSAID combined with antiplatelet medication(s) without PPI use	Applicable through review of medication charts
Antimuscarinic/Anticholinergic Drug Burden (ACB)	
Concomitant use of ≥ 2 medications with antimuscarinic/anticholinergic properties (anticholinergic burden (ACB) score ≥ 4)	Applicable through review of medication charts and calculation of ACB score (ACB score calculator)

Table SII. Ranking of medication use near end of life.

Rank	Drug	Percent
1	Omepraole	9.40%
2	Dobutamine/Noradrenaline/epinephrine	6.30%
3	Salbutamol/Ipratropium/budesonide	5.91%
4	Atorvastatin	4.36%
5	Enoxaparin	4.07%
5	Paracetamol	4.07%
5	Dexamethasone/hydrocortisone/methylprednisolone/prednisolone	4.07%
6	Acetylsalicylic acid	3.97%
6	Furosemide/torasemide	3.97%
7	Unfractionated heparin	3.88%
8	Soluble insulin/isophane insulin	3.39%
9	Fluconazole	3.00%
10	Lactulose	2.91%
11	Aluminium hydroxide, magnesium hydroxide and oxethazaine	2.42%
11	Amlodipine	2.42%
12	Acetylcysteine	2.03%
13	Bisoprolol	1.94%
13	Fentanyl	1.94%
14	Clopidogrel	1.65%
15	Midodrine	1.55%
16	Apixipban	1.36%
16	Digoxin	1.36%
17	Etamsylate	1.26%
18	Vitamin K	1.16%
19	Fondaparinux	1.07%
19	Octreotide	1.07%
19	Sodium picosulfate and magnesium citrate/docusate sodium	1.07%
20	Levetiracetam	0.97%

Table SII. Ranking of medication use near end of life.

21	Glycerin suppositories	0.87%
21	Nitroglycerin	0.87%
21	Carvedilol	0.87%
21	Nebivolol	0.87%
21	Captopril/enalapril/ramipril	0.87%
21	Tamsulosin/doxazosin	0.87%
22	Spironolactone	0.78%
22	Allopurinol	0.78%
23	Phenytoin	0.58%
23	Tramadol	0.58%
23	Mannitol	0.58%
24	Granisetron hydrochloride	0.48%
24	Slimarin	0.48%
24	Oral Glycerol	0.48%
25	Famotidine	0.39%
25	Rhubarb extract, senna leaf, purified sulphur, and wood charcoal	0.39%
25	Quetiapine	0.39%
26	Tranexamic acid	0.29%
26	Epoetin alfa	0.29%
26	Ursodeoxycholic acid	0.29%
26	Trimetazidine	0.29%
26	Pentoxifylline	0.29%
26	Levothyroxine	0.29%
26	Zolindronic acid	0.29%
27	Acyclovir	0.19%
27	Cilostazol	0.19%
27	Itopride	0.19%
27	Propranolol	0.19%
27	Bromohexine	0.19%
27	Valproic acid	0.19%
27	Escitalopram	0.19%
27	Cerebrolysin	0.19%
27	Citicoline	0.19%
27	Carbimazole	0.19%
27	Febuxostat	0.19%
28	Remdesivir	0.10%
28	Ivermectin	0.10%
28	Warfarin	0.10%
28	Rebamipide	0.10%
28	Domperidone	0.10%
28	Cholestyramine	0.10%
28	Diltiazem	0.10%

Table SII. Ranking of medication use near end of life.

28	Hydrochlorothiazide, olmesartan/amlodipine, valsartan, hydrochlorothiazide	0.10%
28	Amiodarone	0.10%
28	Terbutaline	0.10%
28	Carbamazepine	0.10%
28	Mirtazapine	0.10%
28	Memantine	0.10%
28	Propofol	0.10%
28	Midazolam	0.10%
28	Eszopiclone	0.10%
28	Piracetam	0.10%
28	Carbidopa and levodopa	0.10%
28	Bicalutamide	0.10%
28	Finasteride	0.10%
28	Chymotrypsin	0.10%
28	Cetirizine	0.10%
29	Ticagrelor	0.00%
29	Aripeprazol/pantoprazole	0.00%
29	Mebeverine/sulpiride	0.00%
29	Tiemonium methylsulfate	0.00%
29	Pinene, camphene, cineol, menthone, menthol, borneol, and olive oil	0.00%
29	Nimodipine	0.00%
29	Acetazolamide	0.00%
29	Methyldopa	0.00%
29	Ivabradine	0.00%
29	Pipazethate	0.00%
29	Theophylline	0.00%
29	Donepezil	0.00%
29	Meclofenoxate	0.00%
29	Amantadine	0.00%
29	Calcitonin	0.00%
29	Gliclazide	0.00%
29	Metformin	0.00%
29	Dapagliflozin	0.00%
29	Piperazine citrate, colchicine crystals, and atropine sulphate	0.00%
29	Colchicine	0.00%