

High-Risk Perioperative Medications in the Chinese Elderly Population

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Background: Inappropriate perioperative medications among elderly patients increase the risk of adverse events and undermine surgical outcomes. This study aimed to assess the prevalence of high-risk medications in elderly surgical patients and verify the effectiveness of a new-developed high-risk perioperative medications (HRPOMs) list for the elderly.

Methods: A cross-sectional, single-center study was conducted at Jinshan Hospital of Fudan University. A total of 810 elderly surgical patients were included in the study. The HRPOMs list was applied to patients' data to identify the HRPOMs including chronic medications and medications related to surgery.

Results: A total of 2113 HRPOMs were identified in 810 patients who fulfilled the inclusion criteria. Of these, 1067 (50.5%) involved medications related to surgery, and 982 (46.5%) involved chronic medications. The prevalence of HRPOM exposure, which was defined as at least one HRPOM was 76.3%. Patients that were 70 years or older (adjusted odds ratio [AOR] =2.118, 95% confidence interval [CI], 1.420~3.159), hospitalized over two weeks (AOR =4.192, 95% CI, 1.493~11.771), with more than 2 distinct diagnoses (AOR =3.407, 95% CI, 2.224~5.220) and with 16 or more medications during hospitalization were more likely to be exposed to HRPOMs. Patients who underwent surgeries of Grade IV were at 1.73 increased odds of HRPOM exposure compared with those who received surgeries of Grade III or lower (P=0.071).

Conclusion: HRPOMs are more common in patients of 70 years or older, with 3 or more distinct diagnoses, with 16 or more medications and hospitalized for 15 days or longer. Our study showed the validity of the HRPOMs list in the perioperative medication review for the elderly and may induce further research to reveal the impact of HRPOMs upon the surgical outcomes of the elderly.

Keywords: prevalence, high-risk perioperative medication, elderly, China

Introduction

With the progress of medical technology, an ever-increasing number of operative procedures are performed in patients, especially in aged patients. Compared with their younger counterparts, the older surgical patients encounter a higher risk of perioperative complications and mortality due to deteriorated physical function and surgical stress.^{1,2} Additionally, the elderly are susceptible to multiple comorbid conditions and have to take chronic medications. The inappropriate withdrawal or withholding of chronic medications in perioperative period is associated with an increased risk for drug-related problems (DRPs), including medication errors and adverse events.^{3,4} Also, the adverse interactions between chronic medications and medications related to surgeries, for instance, anesthetics, analgesics, antibiotics

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and contrast agents, jeopardize surgical outcomes for the aged patients.⁵ For these reasons, it is necessary to review the perioperative medications for the elderly all along the care pathway to identify drugs that potentially imperil the safety of the patients.

A medication review refers to the structured evaluation of a patient's medication regime to provide convenience in minimizing the number of the DRPs and optimizing the patients' outcomes. A few published studies have established tools for reviewing the elderly patients' medication regimes and optimizing the patients' pharmacotherapy. Most of these tools are based on explicit criteria, including the Beers criteria,⁶ The Screening Tool for Older Person's Prescription (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) criteria,⁷ Priscus List,⁸ Australian Prescribing Indicators Tool,⁹ French Consensus Panel List,¹⁰ Zhan's criteria¹¹ and Improved criteria in the elderly tool.¹² These criteria were mostly used to assess the elder medical patients' medication rather than surgical ones', for they failed to evaluate the interactions between medications and perioperative physical and pathological conditions as well as interactions between chronic medications and surgery-related medications. Whereas, a few clinical studies have researched the chronic medication withdrawal and withholding in the perioperative period.^{13–20} These preexisting studies focused on the impact of specific medication categories upon surgical patients yet did not provide an explicit evidence-based medication list to guide prescribing and medication audit.

Under the circumstances, Chinese experts have developed an explicit criterion as the tool for reviewing high-risk perioperative medications (HRPOMs) for the elderly.²¹ The HRPOMs are defined as (i) drugs that easily cause toxicity or adverse reactions due to aging physical function and surgical stress, (ii) drugs whose inappropriate withdrawal or continuation in the perioperative period easily causes more harm than benefit, (iii) drugs that can be replaced with safer alternatives. A few previous studies have demonstrated that HRPOMs can undermine the physical function or worsen the pathological conditions,^{13,22} postpone or exacerbate the recovery of the surgical wound,^{15,23} and impair the treatment of surgical complications.²⁰

Whereas, there was no literature verifying the HRPOM list, and assessing the prevalence of HRPOMs for the elderly so far. This cross-sectional study aimed to screen the HRPOMs and the association between HRPOM

exposure and the demographic and clinical characteristics of the older patients admitted to a Chinese university-affiliated general hospital, and verify the effectiveness of the new-developed HRPOM list.

Methods

The study population comprised consecutive admissions to the surgical wards of a general hospital over a 6-month period (January 2020–June 2020). All patients aged ≥ 65 years were eligible for inclusion. The medication list for each patient included medications prescribed after the admission and drugs, which were taken before the admission for chronic diseases. The solvents and traditional Chinese medicines were excluded. Demographics and clinical characteristics were obtained using the Hospital Information System, included patient demographics, the number of diagnoses at discharge, day of hospital stay and the magnitude of the surgery. As some patients were admitted more than once to the hospital during the study period, calculations were based on admissions rather than patients. Screening for HRPOMs for the elderly was performed with the Microsoft Excel Visual Basic for Applications and was manually reviewed by 2 clinical pharmacists (Ren and Tan).

Chi-square analysis was used for univariate analysis and multivariate logistic regression analysis was used to establish the association between HRPOM exposure, which is defined as at least one HRPOM, and both demographic and clinical variables (expressed as odds ratio with 95% confidence intervals, [CI]). Statistical analysis was conducted using the SPSS software package version 25 (SPSS, Chicago, IL). Figures were drawn using the GraphPad Prism version 9.00 for Windows, GraphPad Software, San Diego, California, USA.

An ethics committee review was not required as the study was a clinical audit, and the patient data was anonymized to comply with relevant data protection and privacy regulations.

Results

Between January 1st 2020 and June 30th 2020, 810 patients were admitted to Jinshan Hospital of Fudan University to undergo surgery. All patients were included in the study and 618 (76.3%) of them encountered HRPOM exposure. In total, 19,224 medications including chronic medications and medications prescribed after the admission were used by the 810 patients, and 2113 HRPOMs were identified (11.0%).

Table 1 Demographics and Clinical Characteristics of the Study Population in Jinshan Hospital of Fudan University, Shanghai, China, Between Jan 1st and June 30th, 2020

Patient Characteristics and Clinical Data	N (%)	HRPOMs(%)
Sex, n (%)		
Female	399 (49.3)	273 (48.2)
Male	411 (50.7)	293 (51.8)
Age		
65~69	296 (36.5)	191 (30.9)
≥70	514 (63.5)	427 (69.1)
Number of distinct diagnosis		
1~2	233 (28.8)	120 (19.4)
3~5	356 (43.9)	296 (47.9)
≥6	221 (27.3)	202 (32.7)
Days of hospital stay		
≤7	423 (52.2)	263 (42.6)
8~14	221 (27.3)	194 (31.4)
≥15	166 (20.5)	161 (26.1)
Number of medications		
≤15	219 (27.0)	97 (15.7)
16~24	286 (35.3)	229 (37.1)
≥25	305 (37.7)	292 (47.2)
Grade of surgeries		
Surgeries of level I,II,III	594 (73.3)	420 (68.0)
Surgeries of level IV	216 (26.7)	198 (32.0)

Table 1 reports the demographics and clinical characteristics and the presence of HRPOM exposure. The mean age (\pm standard deviation, [SD]) of patients was 73.3 (\pm 6.7, range: 65–95), 50.7% were males. The mean day of hospital stay was 9.9 days (\pm 10.1, range: 0–122). The mean number of distinct diagnoses at discharge was 4.5 (\pm 3.1, range: 1–19). The mean number of medications used during hospitalization was 23.7 (\pm 14.3, range: 1–101). The magnitude of surgery was categorized into 4 groups according to the Surgical Classification Management System of China.²⁴ Figure 1 shows the distribution of the magnitude of the surgery and HRPOM exposure. The type of surgery was classified according to the International Classification of Diseases Clinical Modification of 9th Revision Operations and Procedures (ICD-9-CM-3), including general surgery (36.3%), ophthalmology (6.9%), otolaryngology (4.7%), gynecology (3.3%), neurosurgery (6.7%), urology (10.1%), orthopedics (23.7%) and thoracic surgery (8.3%).

The contribution of HRPOMs identified is showed in Table 2. 2113 HRPOMs which were identified in the study

involved 42 medications and 12 categories including of cardiovascular system (20.9%), urinary system (12.6%), hematological system (17.2%), central nervous system (10.9%), endocrine system (17.4%), gastrointestinal system (2.7%), 1st-generation anti-allergic (3.4%), anesthetics or anesthesia-assisted (1.6%), anti-inflammatory and anti-rheumatic (12.4%), anti-infective (0.7%), respiratory (0.1%) and other medications (0%). As shown in Figure 2, the top 20 medications comprised 93.5% of the HRPOMs.

Table 3 reports the crude and adjusted odds for the occurrence of HRPOM exposure according to the variables. Upon univariate analysis, patients who were 70 years or older, or stayed in the hospital longer than 7 days were at higher risk of HRPOM exposure. The female patients were more likely to encounter HRPOM exposure than the male patients. Those with HRPOM exposure at discharge were significantly more likely to have more than 2 diagnoses or to use more than 15 medications during their hospitalization. Additionally, patients who underwent surgeries of Grade IV suffered more likelihood of HRPOM exposure than those who underwent surgeries of Grade III or lower.

Multivariate analysis showed there were positive associations between HRPOM exposure and age, the number of diagnoses at discharge, days of hospital stay and the number of medications used during hospitalization. Besides, patients who underwent surgeries of Grade IV were at 1.73 times increased odds of HRPOM exposure.

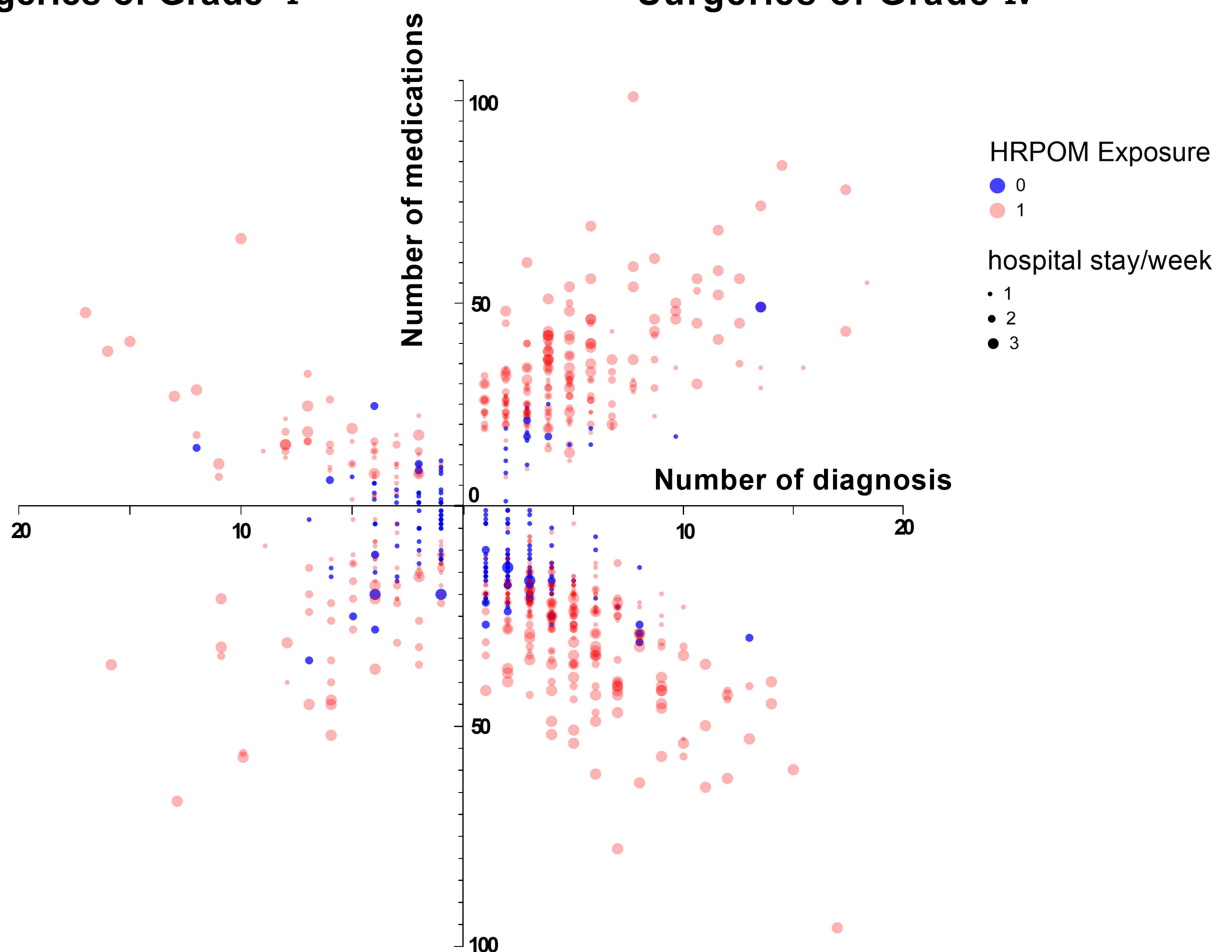
Discussion

The objective of our study was to investigate the previously unidentified prevalence of HRPOM exposure for the elderly in a Chinese university-affiliated general hospital, and verify the new-developed HRPOM list for the elderly. To our knowledge, this study is the first attempt to use a Chinese representative sample regarding the elderly surgical patients admitted to 8 common surgical wards to estimate the prevalence of HRPOMs with the use of a new-developed list of HRPOMs for the elderly. During our study, application of the HRPOM list had not yet been published for any settings.

Our findings revealed a total number of 2113 HRPOMs in a total number of 19,224 medications, and 618 participants encountered HRPOM exposure (76.3%). The preexisting medication review concerning perioperative medication for the elderly is limited. 486 participants in our study encountered HRPOMs related to chronic

Surgeries of Grade I

Surgeries of Grade IV



Surgeries of Grade II

Surgeries of Grade III

Figure 1 The distribution of the number of diagnosis and medications, hospital stay per week and HRPOM exposure according to the magnitude of surgery.

Notes: Hospital stay/week: 1: ≤ 7 days, 2: 8–14 days, 3: ≥ 15 days. The occurrence of HRPOM exposure of patients with surgeries of Grade IV was 91.7% compared with 66.3% for those with surgeries of Grade I, 62.8% for those with surgeries of Grade II and 74.0% for those with surgeries of Grade III.

diseases (60.0%), while the previously reported prevalence of potentially inappropriate medications (PIMs) in Chinese hospitalized older patients ranged from 53.5% to 72.5%,^{25,26} whereas few literature showed the prevalence of PIM in surgical patients was from 42.3% to 77.6%.^{27–29} The HRPOM list for the elderly complies well with previously published PIM criteria.

HRPOMs generally included two supercategories in our study, drugs related to surgery such as analgesics, anesthetics, sedatives and anti-infective agents and drugs related to chronic non-communicable diseases such as antihypertensives, hypoglycemics and antimycardial ischemia agents. HRPOMs related to surgery in our study comprised 50.5% while 46.5% for HRPOMs related to chronic non-communicable diseases. Drugs related to

surgery usually involve anesthesia, induced anesthesia and post-surgical complications such as pain, delirium, bleeding, thrombosis and infection. In the first place, the HRPOMs referred to non-steroidal anti-inflammatory drugs (NSAIDs, aspirin ≤ 100 mg/day excluded) that were used by 257 participants (31.7%). The utilization rate of NSAIDs in our study was much higher than what was reported in previous literature regarding geriatric medication^{26,30,31} mainly due to their foundational role in postsurgical analgesic, anti-inflammatory, anti-stress³² and anti-fever. Whereas the short-term use of postsurgical NSAIDs is associated with increased risk of bleeding³³ and acute kidney injury³⁴ especially in the older population and/or patients with related underlying medical conditions. The second-most HRPOM related to surgery was

Table 2 HRPOMs and the Concomitant Conditions and Potential Risks Identified in the Study and Recommendations According to the List

Class	Conditions	Potential Risks	Recommendation	Number (%)
Cardiovascular system medications				
Beta-blocking agents	/	Withdrawal increases the risk of angina exacerbation, myocardial infarction or even sudden death, Continued using can reduce the incidence of postoperative atrial fibrillation and avoid withdrawal syndrome	1.Continue to use during the perioperative period 2.Pay attention to monitoring blood pressure and pulse	69(3.3%)
Alpha-adrenoreceptor antagonists	General anesthesia	Increases risk of postural hypotension and bradycardia	1.Closely monitor blood pressure during the surgery 2.Use with caution after surgery	5(0.2%)
ACEI/ARB	Potassium-sparing diuretics	Increases risk of hyperkalemia	Avoid combining Potassium-sparing diuretics (except patients with hypokalemia)	220(10.4%)
	Non-cardiac surgery	Potential hypotension risk during induction of anesthesia	Use with caution during the perioperative period, pay attention to monitoring blood pressure and electrolyte levels	
Organic nitrates	/	Continued using helps control blood pressure and angina, but affects intraoperative blood pressure	Continue to use, pay attention to monitoring intraoperative blood pressure	122(5.8%)
Antiarrhythmics, class III (amiodarone)	/	Severe arrhythmia (QT interval prolongation and torsades de pointes); Withdrawal can not control arrhythmia symptoms	Closely monitor ECG	20(0.9%)
	Halogenated inhalation anesthetics	Risk of enhanced myocardial inhibition and conduction, increases risk of postoperative acute respiratory distress syndrome (ARDS)	Use halogenated inhaled anesthetics with caution during the surgery	
Rauwolfia alkaloids (reserpine)	/	Increases the risk of refractory hypotension during the surgery	Stop 1–2w before surgery, for emergency/limited surgery, prepare for norepinephrine	2(0.1%)
Digoxin>0.125mg/d	/	Arrhythmia	Use with caution, pay attention to monitoring the concentration of digoxin and potassium level	4(0.2%)
Urinary system medications				
Thiazines	/	Affects electrolytes and blood volume levels	Continue to use, pay attention to monitoring blood pressure and electrolyte levels	53(2.5%)
Loop diuretics	/	Affects electrolytes and blood volume levels, increases risk of electrolyte imbalance and hypotension	Stop on the day of surgery or discretion according to the specialist situation	178(8.4%)

(Continued)

Table 2 (Continued).

Class	Conditions	Potential Risks	Recommendation	Number (%)
Potassium-sparing diuretics	/	Increases risk of hyperkalemia	Stop on the day of surgery or discretion according to the specialist situation, monitor Potassium levels	36(1.7%)
Hematological system medications				
Clopidogrel	/	Increases risk of bleeding	Comprehensive assessment, if you need to stop, stop 5–7d before surgery	40(1.9%)
Cilostazol	/	Increases risk of bleeding	Comprehensive assessment, if you need to stop, stop 3–5d before surgery	8(0.4%)
Warfarin	Elective surgery	Increases risk of bleeding	Stop 3–5d before surgery, monitor INR (ideally ≤ 1.5) and bleeding situation	5(0.2%)
Low molecular weight heparin	/	Increases risk of bleeding	1.Therapeutic: stop 24h before surgery 2.Prophylaxis: stop 12h before surgery 3.Discretion according to the specialist situation	126(6%)
Asprin (≤ 100 mg/day)	/	Increases risk of bleeding	Use with caution and monitor bleeding situation	76(3.6%)
Heparin	/			36(1.7%)
Rivaroxaban	/			73(3.5%)
Central nervous system medications				
Benzodiazepine derivatives	/	Increases risk of delirium, fall, cognitive impairment and hypotension	Use with caution during the perioperative period; monitor blood pressure	103(4.9%)
Z-drugs	/	Increases risk of delirium, fall and cognitive impairment	Use with caution during the perioperative period	2(0.1%)
Phenothiazines (perphenazine)	/	Can enhance CNS depression, lower seizure threshold, cause ECG abnormalities, arrhythmias, hypotension, neuroleptic malignant syndrome; discontinuation associated with withdrawal dyskinesia and rebound agitation	Continue to use with caution during the perioperative period, pay attention to monitoring	4(0.2%)
Phenothiazines (chlorpromazine)	/	Increases risk of delirium	Use with caution during the perioperative period	2(0.1%)
	General anesthesia	Increases risk of postural hypotension and bradycardia	1.Closely monitor blood pressure during the surgery 2.Use with caution after surgery	

(Continued)

Table 2 (Continued).

Class	Conditions	Potential Risks	Recommendation	Number (%)
Dexmedetomidine	/	Increases risk of hypotension and non-fatal cardiac arrest	Closely monitor blood pressure and pulse	111(5.3%)
SSRIs	/	Nervous system adverse reactions (insomnia, dizziness, unconsciousness, upset and agitation)	Pay attention to the symptoms of the nervous system	5(0.2%)
Anti-Parkinson drugs (levodopa and benserazide)	Halothane anesthesia	Increases intraoperative blood pressure fluctuations and risk of arrhythmia	Stop 12–48h before surgery	3(0.1%)
Endocrine system medications				
Glucocorticoids	NSAIDs	Increases risk of bleeding	Monitoring bleeding situation	189(8.9%)
Metformin	Renal insufficiency	Increases risk of lactic acidosis	Stop 48h before surgery	50(2.4%)
	Intraoperative venous contrast		Monitor renal function after 2–3 days of radiography and restart after normal results	
Quick/Short-acting insulin	Surgery requiring fasting water	Increases risk of hypoglycemia	Stop on the day of surgery	92(4.4%)
Sulfonylureas	Surgery requiring fasting water	Increases risk of hypoglycemia	Stop on the day of surgery	24(1.1%)
Non-sulfonylureas	Surgery requiring fasting water	Increases risk of hypoglycemia	Stop on the day of surgery	8(0.4%)
Thiazolidinediones	/	Increases risk of hypoglycemia and postoperative fluid retention	Stop on the day of surgery	4(0.2%)
Gastrointestinal system medications				
Scopolamine	/	Increases risk of delirium and cognitive impairment	Use with caution during the perioperative period	58(2.7%)
Antiallergic medications, 1st-generation				
Promethazine	/	Increases risk of delirium and potentially enhances the sedative effect of general anesthetics	Stop 1d before surgery	11(0.5%)
Chlorphenamine	/			62(2.9%)
Anesthetics or anesthesia-assisted medications				
Propofol	Serious heart disease (ejection fraction <50%)	Increases risk of serious cardiovascular adverse reactions	Closely monitor circulatory function during the perioperative period	7(0.3%)
Rocuronium Bromide	Impaired liver function	Mainly excreted by bile, prone to accumulation	Avoid using drugs that aggravate liver damage during the surgery	2(0.1%)
Pethidine	/	Increases risk of fall, seizure and delirium	Avoid using during the perioperative period	24(1.1%)

(Continued)

Table 2 (Continued).

Class	Conditions	Potential Risks	Recommendation	Number (%)
Anti-inflammatory and anti-rheumatic medications				
NSAIDs (Aspirin ≤ 100mg/day excluded)	Renal insufficiency	Retention of water and sodium, can aggravate or cause kidney failure	Avoid using during the perioperative period	6(0.3%)
	Major orthopedic surgery	Increases risk of bleeding and kidney damage	Stop 4–7d before surgery or discretion according to the specialist situation	251(11.9%)
Colchicine	/	The therapeutic index is narrow and can cause muscle weakness and polyneuropathy in the setting of renal impairment or drug interactions	Stop on the day of surgery	4(0.2%)
Anti-infective medications				
Vancomycin, aminoglycosides	/	Increases risk of kidney damage	Monitor renal function	11(0.5%)
Linezolid	Sympathomimetic drugs	Increases risk of hypertensive crisis	Avoid using together	4(0.2%)
	Meperidine	Increases risk of 5-HT syndrome	Avoid using together	
Respiratory medications				
Xanthines (aminophylline)	/	The therapeutic window is narrow, can cause arrhythmia and neurotoxicity if drug levels become supratherapeutic	Stop 24h before surgery or discretion according to the specialist situation	2(0.1%)
Other medications				
Rituximab	/	Potential risk of infection	Depending on the drug, stop at two half-lives or at least one dosing interval before surgery	1(0%)

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers; ECG, electrocardiogram; INR, international normalized ratio; Z-drugs, non-benzodiazepine receptor agonists, referred to dexzopiclone, zolpidem and zaleplon; CNS, central nervous system; NSAIDs, non-steroidal anti-inflammatory drugs.

constituted by the glucocorticoids with concomitant NSAIDs (used by 189 participants, 23.3%). Glucocorticoids identified in our study were used to prevent or treat postoperative nausea and vomiting,^{35,36} airway hyperresponsiveness,³⁷ allergy and inflammatory complications. The combination of glucocorticoids and NSAIDs increased the risk of gastrointestinal bleeding and ulcer.^{16,38,39} HRPOMs related to surgery identified in our study potentially increased the occurrence of postoperative complications and thus increased the day of hospital stay and swelled the treatment cost.

Drugs related to chronic diseases were introduced to treat chronic comorbid conditions such as hypertension,

diabetes, heart disease and ischemic stroke. Regarding this supercategory, Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers (ACEI/ARB) for hypertension held the predominant proportion as 220 participants in our study used them (27.2%). Hypertension is the most common chronic disease in Chinese older people, and the incidence was 55.7% for the population aged 65 to 74 years and 60.2% for the population aged 75 years or older.⁴⁰ Our study showed the prevalence of hypertension in the elder surgical patients was 50.2%, which fitted the previous survey. And the utilization rate of ACEI/ARB in our study was 54.1% compared with 27.4% as reported in the survey. Diuretics and calcium channel blockers (CCBs)

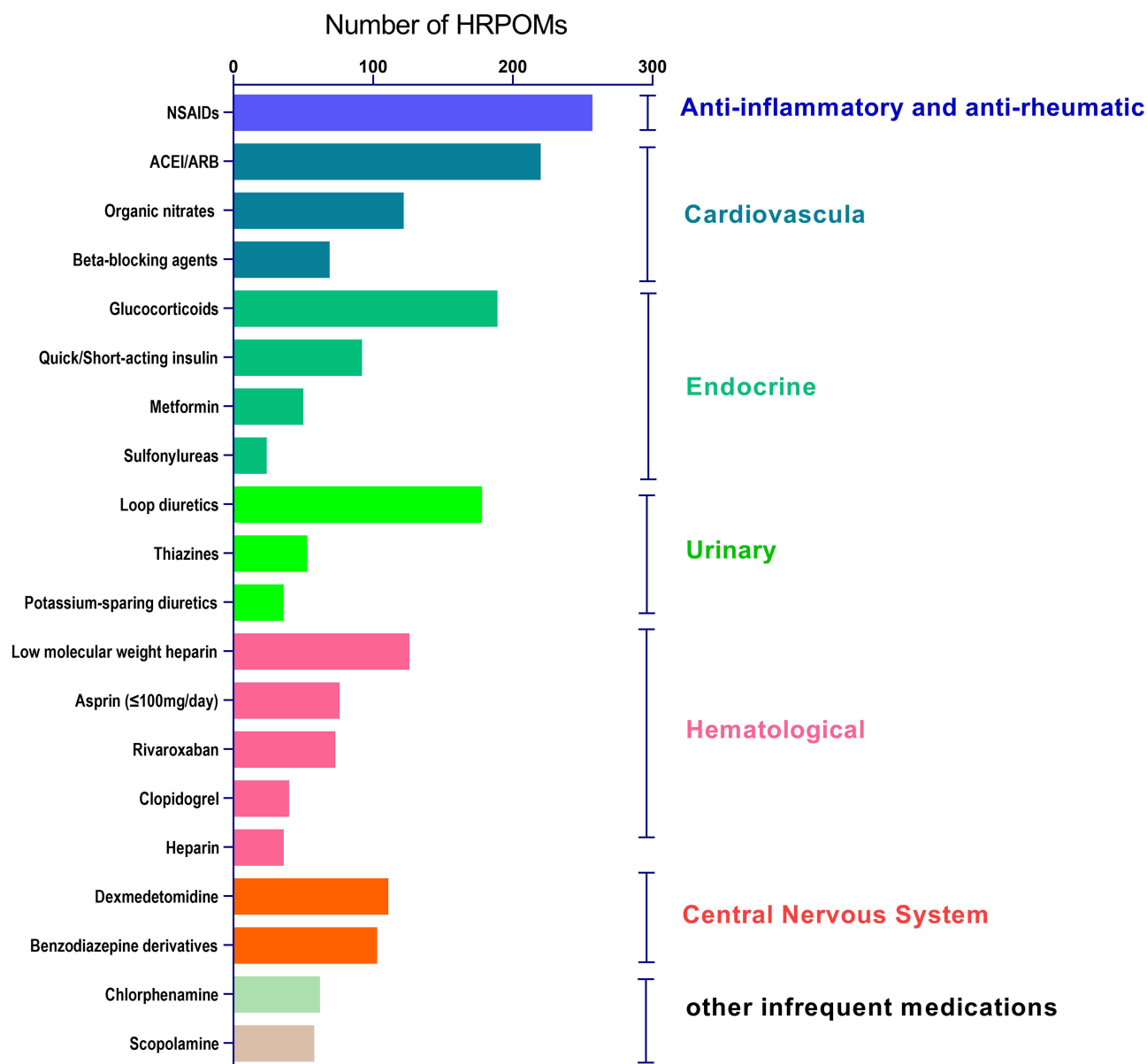


Figure 2 The distribution of the top 20 HRPOMs, which comprised 93.5% of the HRPOMs identified in the study.

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; ACEI, angiotensin-converting enzyme Inhibitor; ARB, angiotensin receptor blocker.

were reported as the two most frequently used antihypertensive agents in China, while our study revealed the perioperative prescription of diuretics was limited mainly owing to their potential effect on electrolytes and blood volume levels. Moreover, according to the HRPOMs list, perioperative use of CCBs was proved to be safe enough except in vasospastic angina patients^{14,41,42} who were not found in this audit. The withholding of ACEI/ARB in the perioperative period was associated with a lower risk of death and postoperative vascular events¹⁹ while a higher prevalence of intraoperative hypotension.⁴³ And when combining with potassium-sparing diuretics, ACEI/ARB

raises the risk of hyperkalemia. Note that the withdrawal of the drugs results in fluctuation of blood pressure. HRPOMs related to chronic diseases were contended to mask the predisposing frailty of patients and/or reduce the severity of chronic comorbidities.¹ Take ACEI/ARB for example, inappropriate withholding or withdrawal of HRPOMs easily brings more harm than benefit.

The demographic and clinical variables were carefully grouped to reveal their associations with HRPOM exposure. Age, the number of distinct diagnoses, days of hospital stay and medications used during hospitalization were independent predictors for HRPOM exposure in our

Table 3 Crude and Adjusted Odds Ratios (95% CI) for HRPOM Exposure in the Study Population in Jinshan Hospital of Fudan University, Shanghai, China, Between Jan 1st and June 30th, 2020

Demographic and Clinical Characteristics	Crude OR of HRPOM Exposure(95% CI), P-value	Adjusted OR of HRPOM Exposure (95% CI), P-value
Sex, n (%), Female Male	0.633(0.456~0.879), P=0.0061	1.013 (0.652~1.575), P=0.954
Age 65~69 ≥70	2.698 (1.937~3.758), P<0.0001	2.118 (1.420~3.159), P<0.0001
Days of hospital stay ≤7 8~14 ≥15	4.371(2.793~6.842), P<0.0001 19.589(7.874~48.738), P<0.0001	1.448(0.844~2.484), P=0.179 4.192(1.493~11.771), P=0.007
Number of distinct diagnoses 1~2 3~5 ≥6	4.646(3.183~6.781),P<0.0001 10.011(5.858~17.110),P<0.0001	3.407(2.224~5.220), P<0.0001 2.938(1.573~5.487), P=0.001
Number of medications ≤15 16~24 ≥25	5.053(3.407~7.493), P<0.0001 28.251(15.255~52.318), P<0.0001	3.738(2.413~5.791), P<0.0001 9.397(4.416~19.996), P<0.0001
Grade of surgeries Surgeries of level I,II,III Surgeries of level IV	4.557(2.726~7.618), P<0.0001	1.730(0.954~3.137), P=0.071

study. The elderly are more likely to be assailed by chronic health conditions, the number and severity of which also increase with age. Moreover, poorly managed chronic diseases often result in other organs' injury and multiple chronic complications, which contributed to the number of distinct diagnoses. Compared with the reference group, patients with 3 or more diagnoses were around 3 times likely to experience HRPOM exposure in our study, which agreed with PIM presence in hospitalized medical patients reported previously.⁴⁴ Medical patients prefer pharmacotherapy rather than non-drug methods to treat each distinct diagnosis and thus receive more high-risk medications,²⁶ whereas surgical patients are more positive to surgical approaches for each distinct diagnosis.

It is noticeable that the occurrence of HRPOM exposure significantly increased with the number of medications in our study. The mean number of drugs used during hospitalization was 23.7, which was far more than the number defined by polypharmacy. Polypharmacy was generally defined as taking five or more medications.⁴⁵ This provides further evidence to previous studies that more

medications mean more risks.^{4,26–29,31} Given the poor health status and medication adherence, the elderly on polypharmacy are at higher risk of adverse drug events than the population of younger age or/and without polypharmacy.⁴⁶

The days of hospital stay were usually regarded as one of the hospitalization outcomes, while in our study this variable also contributed to HRPOMs. Patients hospitalized over two weeks were about 4 times more odds of HRPOM exposure than those hospitalized within one week. The elderly are susceptible to malnourished status, chronic conditions and surgical complications and thus easily suffered from extended length of hospital stay.⁴⁷ Nevertheless, patients with an excessive length of hospital stay are vulnerable to complications such as stress and deep venous thrombosis,⁴⁸ which increased the presence of high-risk medications as reported in preexisting literature.^{27,31}

Surgeries were categorized into four groups according to the magnitude of the surgery, and surgeries of Grade IV were of the highest risk of postsurgical complications and

mortality. Logistic regression revealed HRPOM exposure was scarcely associated with the magnitude of surgery. Patients who underwent surgeries of Grade IV were at 1.73 times increased odds of HRPOM exposure than those with surgeries of Grade III or lower. Kennedy et al also reported a scarce association between postsurgical complications and the magnitude of surgery.¹ Further, the *t*-test showed patients with surgeries of Grade IV possessed more diagnoses, used more medications and hospitalized for more days compared with those of the reference population. As discussed above, the magnitude of surgery contributed to HRPOM exposure via the increasing days of hospital stay and the number of distinct diagnoses and medications.

The limitations of this study must be acknowledged. First, this medication audit was conducted from a resource within a single hospital and thus biases preexist in the spectra of surgeries and other clinical variables. Participants from some surgical wards tended to undergo day-surgeries or lower magnitude of surgeries and thus used fewer medications. HRPOM exposure of these participants was relatively fewer. Second, information from this analysis was limited because hospital records are not designed for research purposes, and their diagnostic quality may vary depending upon each surgeon and clinical unit, as data on surgical outcomes including postsurgical complications and mortality was not recorded. Thus, the impact of HRPOMs upon surgical outcomes remains unclear.

Even though this is the first study to reveal the high-risk medications used in the perioperative period for elderly patients in China, further research is necessary. Studies that use data from multiple medical centers would avoid static biases. And well-designed prospective studies including postsurgical complications and other clinical characteristics that we failed to collect would help to elucidate the impact of HRPOMs on the older surgical patients and further validate the HRPOMs list for the elderly.

Conclusion

We have uncovered the prevalence of HRPOMs for the elderly in a Chinese general hospital, and verified the HRPOM list for the elderly. HRPOMs were found to be more common in patients of 70 years or older, and those with more diagnoses, medications and days of hospital stay were at more odds to expose to HRPOMs. The magnitude of surgery was scarcely associated with HRPOM exposure. HRPOMs identified in our study comprehensively comprised not only chronic medications but also

medications related to surgery. The effectiveness of the HRPOM list for the elderly was thus verified. Our study may provoke prospective research to assess the adverse effects of high-risk medications on the elderly's surgical outcomes. And pharmaceutical care should be applied to monitor drug-related complications of elderly surgical patients and optimize their surgical outcomes.

Ethics Statement

The ethics approval was waived by the Ethics Committee of Jinshan Hospital, Fudan University in Shanghai, China, as the study was a clinical audit. The patient data was anonymized, and complied with relevant data protection and privacy regulations.

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Disclosure

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