ORIGINAL RESEARCH

Relationship Between Perioperative Medication and Prolonged Postoperative Hospital Stay in Older Adults with Spinal Surgery: a Retrospective Cohort Study

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ABSTRACT

Background

Older people are prone to multiple chronic diseases and, as a result, require multiple medications. At present, there is no study to verify whether the use of high-risk perioperative medications (HRPOMs) will adversely affect postoperative outcomes in the relatively old patient. In this study, we aimed to analyze the risks of HRPOMs for prolonged length of hospital stay (LOS) in advanced-aged (≥ 75 years) patients undergoing spinal surgery.

Methods

Medical records of advanced-aged patients who underwent spinal surgeries were retrospectively reviewed. Patients were divided into those who had prolonged LOS (≥ eight days) versus those who did not (< eight days). The demographics, medical comorbidities, and perioperative medications were analyzed. Univariate and multivariate regression were used to determine perioperative risk factors for prolonged LOS.

Results

A total of 268 patients were included with a median age of 79 years (interquartile range [IQR]=76, 82) and 127 (47.4%) patients had a prolonged LOS. In multivariate logistic analysis, higher body mass index (odds ratio [OR] = 1.116; 95% CI, 1.031–1.209), operation time (OR) = 1.009; 95% CI, 1.005–1.012), and number of postoperative HRPOMs (OR= 1.910; 95% CI, 1.464–2.492) were identified as independent predictors for prolonged LOS. The use of metformin was associated with lower likelihood of prolonged LOS in diabetic patients (OR = 0.365; 95% CI, 0.157–0.846).

Conclusion

Our results indicate that the higher number of postoperative HRPOMs, rather than a specific HRPOMs type, is a risk factor for prolonged LOS. The continued preoperative use of metformin in patients with diabetes has a positive impact on the postoperative outcomes.

Key words: older adults, length of hospital stay, spinal surgery, HRPOM, high-risk perioperative medication, polypharmacy

INTRODUCTION

Low back pain is the most common musculoskeletal problem globally, with a lifetime prevalence as high as 84%.[1] Symptomatic low back pain can lead to loss of function or the inability to perform basic activities of daily living in older people. In situations where nonsurgical treatments fail, spinal surgery becomes a viable option. However, older patients are known to encounter high risk of perioperative complications, mortality, and prolonged length of hospital stay (LOS).[2-5] Previous studies have shown that age,[6] morbid obesity, metabolic syndrome,[7] and preoperative benzodiazepine use[8] were independent predictors of prolonged LOS after

spinal surgery. Additionally, older people are susceptible to multiple comorbid conditions and have to take multiple medications (polypharmacy). Hospitals tend to discontinue certain medications that are considered inappropriate during the perioperative period. However, such withdrawal or withholding of chronic medications was found to be associated with an increased risk for drug-related problems (DRPs).[9,10] For these reasons, it is necessary to review the perioperative medications for older patients all along the care pathway, to identify drugs that potentially imperil the safety of the patients.

In 2019, experts in the China Gerontology Pharmaceutical Alliance have developed an explicit criterion as a tool for reviewing the high-risk perioperative medications (HRPOMs) for older patients[11] (Appendix A). It was the first recommendation to provide guidance on older patient-specific HRPOMs. The recommendation provided a list of HRPOMs that may affect the postoperative outcomes in older patients, and reached a consensus on potential strategies to avoid the associated risks. This recommendation largely fills the gap in geriatric surgery, particularly from the perioperative drug management perspective. It has a narrower list of HRPOMs than that of the American Geriatrics Society (AGS) Beers Criteria,[5] which is an explicit list of potentially inappropriate medications (PIMs) for older adults, and provides drug-specific recommendations.

The recommendation provided for HRPOMs has been endorsed in China. Previous studies have found that 76.3% of older patients undergoing surgery used the HRPOMs.[12,13] Studies suggested an increase in the HRPOMs use to be associated with a higher probability of drug risks.[14] However, the impact of recommended HRPOMs on advanced-aged patients is still lacking.

In this study, we aimed to investigate the association of the recommended HRPOMs with postoperative outcome in advanced-aged spinal surgery patients. Therefore, we designed a retrospective study to examine the association of perioperative medications (chronic disease medications, intraoperative medications, and postoperative medications) with the postoperative LOS in the older patients undergoing spinal surgery.

METHODS

We conducted a retrospective cohort study of patients aged ≥ 75 years who underwent elective spinal surgery from January 2020 to December 2021 at the Xuanwu Hospital, Capital Medical University, China. The study was approved by the ethics committee of the Hospital. Spinal surgery was defined as undergoing fusion surgeries with instrumentation under general anesthesia. Older patients with conditions such as lumbar disc herniation, lumbar spinal stenosis, cervical spondylotic myelopathy, lumbar spondylolisthesis, or scoliosis underwent spinal surgery.

The primary outcome was the postoperative LOS. Postoperative LOS was defined as the number of days from the surgery till discharge. Postoperative LOS was dichotomized into two groups, Prolonged LOS and Not, using eight days as cut-off, which was the median value for the entire group.

The discharge criteria were as follows: evidence of the primary condition being improved upon surgery and no complaints of discomfort, such as fever; a visual analog scale (VAS) score of less than 3 points for pain assessment, without any form of discharge from the incision, and able to get off the bed and move.

A data collection sheet was used to collect the demographic characteristics (age, gender, body mass index [BMI]) and comorbidities of the relevant patients. The following clinical data was collected: 1) comorbidities: hypertension, hyperlipidemia, diabetes mellitus (DM), ischemic heart disease (IHD), cerebrovascular disease (CVD), solid malignancy, and peripheral vascular disease (PVD); 2) preoperative laboratory values: hemoglobin, serum albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum creatinine (SCr); 3) intraoperative values: operative time and blood loss; 4) the American Society of Anesthesiologists (ASA) score and the age-adjusted Charlson Comorbidity Index (aCCI) score; 5) postoperative LOS; 6) information on postoperative complications; 7) list of current medications for chronic diseases and those prescribed after the admission (intra- and postoperative medications). Screening for HRPOMs was performed with Microsoft Excel Visual Basic for Applications and was manually reviewed by two clinical pharmacists (Shen and Chu).

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) (non-normally distributed continuous variables were expressed as medians [interquartile range]) and categorical variables as the number and percentage of cases. Comparisons between patients with and without prolonged LOS were performed using the Student's *t*-test or the Mann-Whitney U test for numerical data and χ^2 test or Fisher's exact test for categorical data. Independent predictors of prolonged LOS were evaluated with the logistic regression method. The risk factors for prolonged LOS were first evaluated with univariate analysis, and the statistically significant variables $p < .05$ were included in the multivariate analysis with forward conditional elimination method. Data were presented as odds ratios (OR) with 95% confidence intervals (CI).

The Hosmer–Lemeshow test was used to test the goodness of fit for logistic regression models. Discrimination of the model was further assessed by an analysis of the area under receiver operating curve (AUROC). Statistical Package for Social Sciences version 25.0 was used for statistical analyses. A two-tailed p value <.05 was considered significant.

RESULTS

General Characteristics of the Study Population

A total of 268 patients aged ≥ 75 years out of 315 who underwent spinal surgery were included. Of these, 47 were

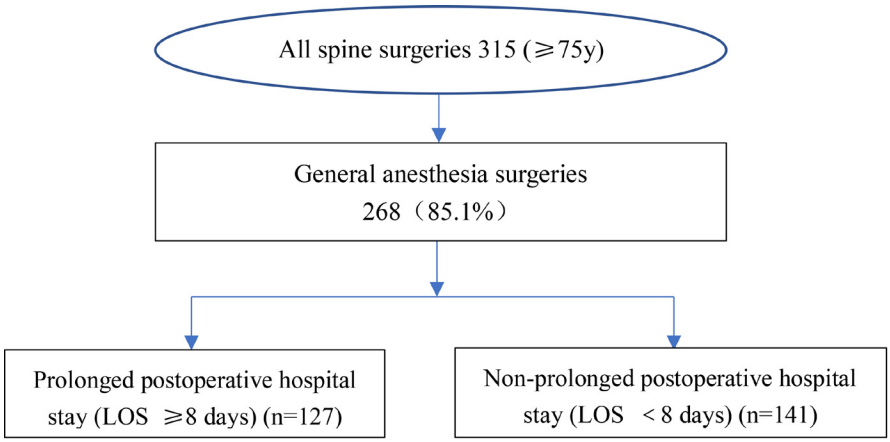

FIGURE 1. The flow chart of the patient selection

excluded because of surgery under epidural anesthesia (Figure 1). The demographic and clinical characteristics were shown in Table 1. The median age of the patients was 79 years (interquartile range, IQR = 76, 82), 42.2% of whom were male and had a mean (± standard deviation) BMI of 24.9 (±3.6) kg/m^2. The median postoperative LOS was 8 (IQR = 7, 13) days. There were 127 (47.4%) patients with prolonged postoperative LOS.

The most common comorbidities were hypertension (63.1%), DM (36.6%), IHD (28.0%), CVD (22.4%), psychiatric conditions (17.2%), PVD (16.0%), and hyperlipidemia (14.2%) (Table 1). A total of 46 patients with 66 types of postoperative complications was reported. The most common complications were cardiac dysrhythmias (3.0%), surgical site infection (3.0%), pneumonia (2.6%), urinary tract infection (2.2%), and acute renal injury (1.9%) (Appendix B).

Perioperative Medications

Preoperatively, 1,580 medications (105 classes) were taken for chronic conditions by the study cohort, of which 785 (29 classes) were identified as HRPOMs. The top five most frequently used drugs were for the treatment of CVDs. Most common HRPOMs were: calcium channel blockers (CCB) (49.6%), angiotensin converting enzyme inhibitors/ angiotensin receptor blockers (ACEI/ARB) (38.1%), antiplatelet agents (specifically aspirin) (29.5%), beta-blocking agents (25.4%), non-steroidal anti-inflammatory drugs (NSAID) (18.7%), thiazide diuretics (15.3%), and organic nitrates (14.2%) (Table 1).

Intraoperatively, 3,553 medications (48 classes) were used, of which 78 (5 classes) were identified as HRPOMs. They were glucocorticoids (79.5%), benzodiazepine derivatives (11.9%), NSAID (11.2%), short-acting insulin (5.2%), and opioid analgesics (0.8%, pethidine 1 and tramadol 1). HRPOMs were rarely used in surgery, so only the impact of the number of medications used in surgery on the postoperative hospital stay was analyzed (Appendix C).

Post-surgically, a total of 3,949 medications (64 classes) were prescribed, of which 624 (17 classes) were identified as HRPOMs. The most frequently used HRPOMs were NSAID (97.8%), glucocorticoids (85.4%), benzodiazepine derivatives (23.1%), and nephrotoxic antibiotic (10.1%) (Table 1).

Factors Associated with Postoperative LOS

Univariate and multivariate analysis were performed to test the association of individual demographic, comorbidity, preoperative laboratory variables, intraoperative variables, and perioperative medication variable with postoperative LOS. In the univariate analysis, higher BMI, surgical site, operation time, blood loss, number of postoperative HRPOMs, postoperative usage of NSAIDs, and glucocorticoids were significantly associated with the LOS and selected for the multivariate regression analysis. In the multivariate analysis, prolonged postoperative LOS was found to be significantly associated with higher BMI (OR = 1.116; 95% CI, 1.031–1.209; p =.007), operation time (OR = 1.009; 95% CI, 1.005–1.012; p < .001) and number of postoperative HRPOMs (OR= 1.910; 95% CI, 1.464– 2.492; p < .001). Preoperative metformin use showed a lower likelihood of having prolonged LOS (OR=0.365; 95% CI, 0.157–0.846; p = .019). There were no significant differences between comorbidities, preoperative laboratory variables, and preoperative medications for chronic diseases, even preoperative HRPOMs (Table 2).

Hosmer–Lemeshow test for multivariate models showed a good fit (χ^2 = 7.263, p = .509). As shown in Figure 2, the AUROC was 0.799.

DISCUSSION

There is an increasing demand of spinal surgery procedures in older adults, particularly due to several disabling degenerative diseases of the spine. LOS is at the core of many quality improvement initiatives because it is directly related to health-care quality and costs.[15,16] Prolonged LOS is also associated with an increased incidence of perioperative complications in older patients.[16,17] Thus, it has become important to elucidate modifiable perioperative risk factors that predict the LOS, especially while considering older patients.

TABLE 1 (part 1 of 2).
Factors associated with prolonged postoperative hospital stay for patients with spine surgery

Variables	*All (n=268)*	*Prolonged Postoperative Hospital Stay*		*P value*
		Yes (n=127)	*No (n=141)*	
Gender (male)	113 (42.2%)	53 (41.7 %)	60 (42.6%)	0.892
Age (years)	79 (76,82)	80 (76, 82)	79 (76, 81)	0.349
Smoking	37 (13.8%)	16 (12.6%)	21 (14.9%)	0.587
BMI(kg/m^2)	24.8 (22.4,27.1)	25.6 (22.8,28)	24.4 (22.2,26)	0.006[a]
Comorbidities				
Hypertension	169 (63.1%)	80 (63%)	89 (63.1%)	0.983
Diabetes mellitus	98 (36.6%)	46 (36.2%)	52 (36.9%)	0.911
Ischemic heart disease	75 (28.0%)	35 (27.6%)	40 (28.4%)	0.770
Cerebrovascular diseases	60 (22.4%)	31 (24.4%)	29 (20.6%)	0.451
Psychiatric conditions	46 (17.2%)	2 (18.9%)	22 (15.6%%)	0.518
Peripheral vascular disease	43 (16.0%)	23 (18.1%)	20 (14.2%)	0.382
Hyperlipidemia	38 (14.2%)	20 (15.7%)	18 (12.8%)	0.485
Arrhythmias	338 (12.3%)	158 (11.8%)	188 (12.8%)	0.854
Immune system diseases	328 (11.9%)	148 (11.0%)	188 (12.8%)	0.709
Solid malignancy	22 (8.2%)	11 (8.7%)	11 (7.8%)	0.798
Laboratory Variables				
Serum hemoglobin (g/L)	125 (118, 134)	124 (119, 133)	126 (117.5, 134.5)	0.857
Serum albumin (g/L)	36.7 (34.8, 38.7)	36.6 (34.7, 38.3)	36.8 (34.8, 38.8)	0.768
Alanine aminotransferase (U/L)	15 (12, 21)	15 (11, 20)	15 (12, 23.5)	0.321
Aspartate aminotransferase (U/L)	21 (18, 25)	21 (18, 25)	21 (18, 25)	0.889
SCr: (mL/min/1.73 m^2) < 60	24 (9%)	10 (7.9%)	14 (9.9%)	0.556
ASA Score	3 (2, 3)	3 (3, 3)	3 (2, 3)	0.080
Acci Score	5 (5,6)	4 (4, 5)	4 (4, 5)	0.508
Surgical Site				0.033[a]
Cervical vertebra	65 (24.3%)	23 (35.4%)	42 (64.6%)	
Thoracic vertebra	5 (1.9%)	4 (80%)	1 (20%)	
Lumbar vertebra	198 (73.9%)	100 (50.1%)	98 (49.5%)	
Intraoperative Characteristics				
Operative time (min)	199 (155, 266)	236 (181.5, 315)	175 (145, 218)	< 0.001[a]
Blood loss (mL)	200 (100, 400)	300 (200, 600)	120 (100, 280)	< 0.001[a]
Pharmaceutical Variables				
Number of HRPOMs for Chronic Disease	3 (1, 4)	3 (2, 5)	3 (1, 4)	0.433
Number of intraoperative medications	13 (11, 15)	13 (11, 15)	13 (11, 15)	0.677
Number of postoperative HRPOMs	3 (2,3)	3 (2, 4)	2 (2, 3)	0.001[a]
HRPOMs for Chronic Disease				
CCB	133 (49.6%)	59 (46.5%)	74 (52.5%)	0.474
ACEI/ARB	102 (38.1%)	49 (38.6%)	53 (37.6%)	0.867
Aspirin	79 (29.5%)	39 (30.7%)	40 (28.4%)	0.675
Beta-blocking agents	68 (25.4%)	35 (27.6%)	33 (23.4%)	0.435
NSAIDs	50 (18.7%)	29 (22.8%)	21 (14.9%)	0.096
Thiazide diuretics	41 (15.3%)	19 (15.0%)	22 (15.6%)	0.884
Benzodiazepine derivatives	41 (15.3%)	24 (18.9%)	17 (12.1%)	0.120
Organic nitrates	38 (14.2%)	21 (16.5%)	17 (12.1%)	0.294
Metformin	37 (13.8%)	12 (9.4%)	25 (17.7%)	0.050[a]
Sulfonylureas	35 (13.1%)	18 (14.2%)	17 (12.1%)	0.608
Clopidogrel	26 (9.7%)	14 (11.0%)	12 (8.5%)	0.488

TABLE 1 (part 2 of 2).
Factors associated with prolonged postoperative hospital stay for patients with spine surgery

Variables	*All (n=268)*	*Prolonged Postoperative Hospital Stay*		*P value*
		Yes (n=127)	*No (n=141)*	
Postoperative HRPOMs				
NSAIDs	262 (97.8%)	127 (100%)	135 (95.7%)	0.019[a]
Glucocorticoids	229 (85.4%)	115 (90.6%)	114 (80.9%)	0.025[a]
Benzodiazepine derivatives	62 (23.1%)	34 (26.8%)	28 (19.9%)	0.180
Vancomycin	25 (9.3%)	25 (19.7%)	0 (0)	< 0.001[a]

[a]Indicates significant difference ($p < .05$).
BMI = body mass index; SCr = serum creatinine; ASA = American Society of Anesthesiologists; aCCI = age-adjusted Charlson Comorbidity Index; HRPOM = high- risk perioperative medication; CCB = calcium channel blockers; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; NSAIDS = non-steroidal anti-inflammatory drug.

One of the potential strategies is to manage inappropriate medications (i.e., those having negative effects in older patients), as older adults are known to have a high burden of polypharmacy.[18,19] We investigated the perioperative medication risk in advanced-aged patients undergoing spinal surgery based on the new HRPOMs recommendation.[11] The goal of our study was to identify the modifiable factors (primarily medications) that were associated with prolonged LOS after spinal procedures in advanced-aged patients. Our results showed two major findings on medication use: 1) Prolonged LOS was not associated with the type and quantity of HRPOMs used to treat chronic diseases before operation, nor with a specific HRPOM after operation, but with the quantity of HRPOMs after operation; and 2) Preoperative use of metformin showed lower likelihood of prolonged postoperative LOS in patients with diabetes.

Previous studies have shown higher BMI to be associated with increase the LOS in patients undergoing spinal surgeries,[20–22] which was also consistent with our findings. In a previous meta-analysis, obese patients had significantly higher incidence of surgical site infections.[23] Larger incision and greater subcutaneous fat thickness in the surgical region have been suggested as issues that increase the risk of infection, due to its anti-inflammatory cytokines followed by insulin resistance.[24] Another study showed that patients with obesity had a significantly lower fusion rate than non-obese patients.[25] It seems that obesity, by putting a mechanical load on the spine and inflammatory factors, affects the musculoskeletal system and eventually delays the fusion rate in the spine.[26]

In this study, we examined the association of intraoperative factors including operation time, intraoperative blood loss, and the use of intraoperative medication with LOS. The average operation time of patients with prolonged LOS was more than 60 minutes longer than that of patients without prolonged LOS, and was an independent risk factor for prolonged hospital stay after operation. This was consistent with a previous study showing that operation time was an independent predictor for prolonged LOS after anterior lumbar interbody fusion.[27] In general, the longer the operation time or the greater amount of blood loss, the larger the operation scale and the more complicated the operation procedure. The patients may need longer recovery time due to the wider scope of surgery, resulting in prolonged LOS.

The primary aim of this study was to analyze whether the use of newly recommended HRPOMs was associated with prolonged postoperative LOS in advanced-aged spinal surgery patients. While considering chronic disease medication, we found that only NSAID had a marginal statistical significance. This may be the result of the small sample size of this study; further verification using a larger sample size is needed. Previous studies have shown that Metformin can reduce all-cause mortality in patients with type-2 diabetes.[28,29] However, less is known about its potential perioperative implications. Metformin in the perioperative phase was associated with the risk of lactic acidosis[30] and is listed as an HRPOM. However, the benefit of proper perioperative glycemic control might outweigh this theoretical risk.[31] Previous studies revealed an association between Metformin prescriptions provided to individuals with type 2 diabetes before a surgical procedure and improved postoperative outcomes,[32-34] which is consistent with our findings, even in advanced-aged surgical patients. Metformin has well-established anti-inflammatory and anti-oxidative properties.[35,36] The pleiotropic advantages of Metformin may positively modulate the inflammatory response to surgical procedures to improve outcomes.[32] However, this needs to be confirmed in well-controlled prospective studies.

We also found that increased numbers of postoperative medications and HRPOMs were independent risk factors for prolonged LOS. It was easy to understand that longer hospital stay is associated with increased postoperative complications, and therefore more medications were needed. The top four postoperative HRPOMs were NSAID, glucocorticoids, benzodiazepines, and vancomycin. Surgeons often used NSAID which could relieve postoperative pain, and glucocorticoids which could reduce tissue edema. Insomnia in elderly patients may worsen after surgery, and the usual treatment is to continue taking benzodiazepines. Interestingly, in this study, 25 patients who used vancomycin after surgery were all in the prolonged postoperative LOS group. After

TABLE 2.
Bivariate and multivariate analysis of risk for prolonged postoperative hospital stay

Variables	*Bivariate Analyses*		*Multivariate Analysis*	
	OR (95%)	*P*	*OR (95%)*	*P*
Gender (male)	1.034 (0.636 -1.681)	.892		
Age (years)	1.034 (0.964 -1.110)	.348		
Smoking	0.824 (0.409 -1.658)	.587		
BMI(kg/m^2)	1.100 (1.026 -1.179)	.007	1.116 (1.031-1.209)	.007[a]
Comorbidities				
Hypertension	0.995 (0.605 -1.634)	.983		
Hyperlipidemia	1.277 (0.642 -2.540)	.485		
Diabetes mellitus	0.972 (0.591 -1.599)	.911		
Ischemic heart disease	0.923 (0.540 -1.579)	.770		
Cerebrovascular diseases	1.247 (0.701 -2.216)	.452		
Solid malignancy	1.121 (0.468 -2.681)	.798		
Peripheral vascular disease	1.338 (0.696 -2.573)	.383		
Laboratory Variables				
Serum hemoglobin (g/L)	0.999 (0.983 -1.014)	.859		
Serum albumin (g/L)	0.989 (0.918 -1.066)	.767		
Alanine aminotransferase (U/L)	0.988 (0.964 -1.012)	.321		
Aspartate aminotransferase (U/L)	0.998 (0.969 -1.027)	.889		
SCr (mL/min/1.73 m^2) < 60	0.775 (0.332 -1.813)	.557		
ASA score	1.563 (0.947 -2.580)	.081		
aCCI score	1.076 (0.867 -1.336)	.506		
Intraoperative Characteristics				
Operative time (min)	1.010 (1.006 -1.014)	< .001	1.009 (1.005 -1.012)	< .001[a]
Blood loss (mL)	1.004 (1.003 -1.005)	< .001		
Pharmaceutical Variables				
Number of HRPOMs for Chronic Disease	1.049 (0.931 -1.181)	.431		
Number of intraoperative medications	1.018 (0.936 -1.107)	.676		
Number of postoperative HRPOMs	1.962 (1.535 -2.508)	< .001	1.910 (1.464 -2.492)	< .001[a]
HRPOMs for Chronic Disease				
CCB	0.841 (0.524 -1.350)	.474		
ACEI/ARB	1.043 (0.637 -1.709)	.867		
Aspirin	1.119 (0.662 -1.893)	.675		
Beta-blocking agents	1.245 (0.718 -2.160)	.436		
NSAID	1.691 (0.908 -3.149)	.098		
Hydrochlorothiazide	0.952 (0.488 -1.854)	.884		
Benzodiazepine derivatives	1.700 (0.866 -3.335)	.123		
Organic nitrates	1.445 (0.725 -2.881)	.296		
Metformin	0.484 (0.232 -1.010)	.053	0.365 (0.157 -0.846)	.019 [a]
Sulfonylureas	1.205 (0.592 -2.453)	.608		
Clopidogrel	1.332 (0.592 -2.998)	.489		
Postoperative HRPOMs				
NSAID	2.701 (1.320 -5.525)	.007		
Glucocorticoids	2.270 (1.096 -4.699)	.027		
Benzodiazepine derivatives	1.475 (0.834 -2.610)	.181		
Vancomycin	—	—		

[a]Indicates significant difference (p < .05).
HR = hazard ratio; BMI = body mass index; SCr = serum creatinine; ASA = American Society of Anesthesiologists; aCCI = age-adjusted Charlson Comorbidity Index; HRPOM = high- risk perioperative medication; CCB = calcium channel blockers; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; NSAIDS = non-steroidal anti-inflammatory drug.

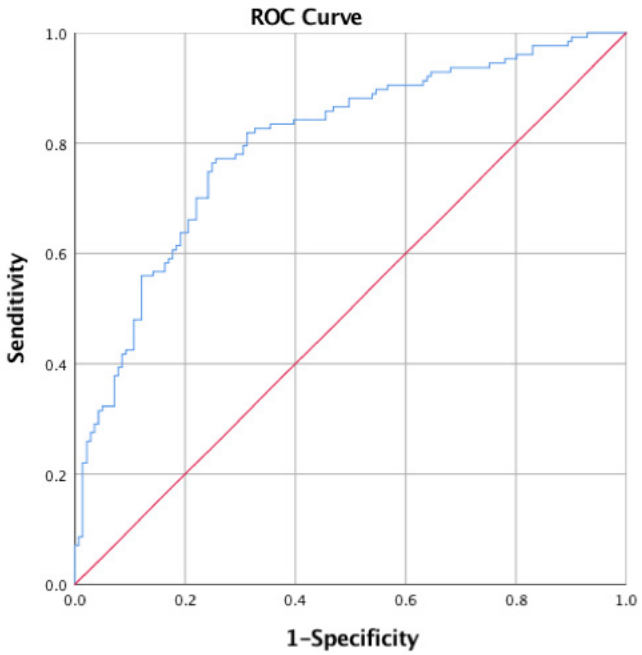

FIGURE 2. Area under receiver operating characteristic curve for prolonged postoperative hospital stay (model included BMI, operative time, number of postoperative HRPOMs and preoperative use of Metformin for analysis)

analyzing the postoperative complications of these patients: seven patients had confirmed or suspected surgical incision infection; eight had confirmed or suspected pulmonary infection; and vancomycin was used to prevent wound infection in four patients following postoperation evalution, because of the high risk of infection. No specific reasons for using vancomycin were reported in the other six patients (Appendix D). In multivariate analysis, no independent risk of these four types of medications was observed for prolonged LOS. However, the number of postoperative HRPOM was an independent risk factor for prolonged LOS. These findings are in line with previous studies suggesting the risk of PIMs on various conditions in older adults.[37,38] Hence, managing polypharmacy, including postoperative medications, could shorten the LOS, irrespective of HRPOMs classes.

The strength of this study was the inclusion of a single type of surgery, thus avoiding the influence of surgical diversity on the outcome. Most importantly, this is the first study to investigate the relationship between HRPOMs (in accordance with a recent guideline) and clinical outcome (which was prolonged LOS) in advanced-aged patients.

This study had the limitation of a retrospective design with limited data availability, such as information on involved levels of spinal surgery, and detailed evaluation of postoperative complications. This study was single-centered, with limited sample size, and lacked a detailed analysis of additional laboratory test results. Large scale prospective studies may be implemented in the future to confirm our findings and take into account additional diseases or conditions that are associated with high use of HRPOMs.

CONCLUSION

Our study showed that the number of postoperative HRPOMs was associated with prolonged LOS after spinal surgery in relatively older patients. Reducing polypharmacy by targeting HRPOMs may be helpful in reducing the postoperative LOS. Metformin may have a positive effect on reducing the postoperative LOS in older diabetic patients. Our results add to the notion of the great importance of a multidisciplinary approach, such as involvement of pharmacists in improving geriatric care, even in surgical settings.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood the *Canadian Geriatrics Journal*'s policy on conflicts of interest disclosure and declare there are none.

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APPENDICES

APPENDIX A (part 1 of 8). The list of high-risk perioperative medications for older patients in China

	Medications or Medication Classes	*Conditions*	*Potential Risks*	*Recommendations*
			Nervous System Medications	
1	Estazolam	——	Increases risk of delirium, fall and cognitive impairment	Use with caution during the perioperative period
2	Lorazepam	——	Increases risk of delirium, fall and cognitive impairment	Use with caution during the perioperative period
3	Diazepam	——	Increases risk of delirium, fall, cognitive impairment and hypotension	Use with caution during the perioperative period; monitor blood pressure
4	Clonazepam	——	Increases risk of delirium, fall and cognitive impairment	Use with caution during the perioperative period
5	Midazolam	——	Increases risk of delirium	Use with caution during the perioperative period
		≤80 years old	Delay in anesthesia recovery	Use with caution during the surgery
6	Zolpidem	——	Increases risk of delirium, fall and cognitive impairment	Use with caution during the perioperative period
7	Zopiclone	——	Increases risk of delirium and fall	Use with caution during the perioperative period
8	Zaleplon	——	Increases risk of delirium and fall	Use with caution during the perioperative period
9	Dexmedetomidine	——	Increases risk of hypotension and non-fatal cardiac arrest	Closely monitor blood pressure and pulse
10	Phenytoin	——	Increases risk of delirium and fall	Continue to use during the perioperative period, pay attention to monitoring
11	Levodopa and Benserazide	Halothane anesthesia	Increases intraoperative blood pressure fluctuations and risk of arrhythmia	Stop 12-48h before surgery
12	Donepezil, Rivastigmine, Huperzine A, Galantamine	——	Increases risk of neuromuscular blockade and postoperative delirium	Avoid new prescriptions during the perioperative period; continue long-term medication with close monitoring; after evaluation, if you need to stop, donepezil stopped 2-3w pre-op, galantamine stopped 24h pre-op
			Anesthetics or Anesthesia-Assisted Medications	
13	Propofol	Serious heart disease (ejection fraction <50%)	Increases risk of serious cardiovascular adverse reactions	Closely monitor circulatory function during the perioperative period
14	Rocuronium Bromide	Impaired liver function	Mainly excreted by bile, prone to accumulation	Avoid using drugs that aggravate liver damage during the surgery
15	Pethidine	——	Increases risk of fall, seizure and delirium	Avoid using during the perioperative period
16	Tramadol	——	Increases risk of seizure and delirium	Use with caution during the perioperative period
		Chronic seizures or epilepsy	Increases risk of seizure	Avoid using during the perioperative period or discretion according to the specialist situation
			Psychiatric Medications	
17	Phenothiazines (perphenazine / fluphenazine / chlorpromazine), butyrophenone (haloperidol), risperidone, olanzapine	——	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

APPENDIX A (part 2 of 8). The list of high-risk perioperative medications for older patients in China

	Medications or Medication Classes	*Conditions*	*Potential Risks*	*Recommendations*
18	Chlorpromazine	——	Increases risk of delirium	Use with caution during the perioperative period
		General anesthesia	Increases risk of postural hypotension and bradycardia	1.Closely monitor blood pressure during the surgery 2.Use with caution after surgery
		Chronic seizures or epilepsy	Increases risk of seizure	Avoid using during the perioperative period or discretion according to the specialist situation
		Parkinson disease	Worsens parkinsonian symptoms	Use with caution during the perioperative period
19	Clozapine	Chronic seizures or epilepsy	Increases risk of seizure	Avoid using during the perioperative period or discretion according to the specialist situation
20	Olanzapine	General anesthesia	Increases risk of postural hypotension and bradycardia	1.Closely monitor blood pressure during the surgery 2.Use with caution after surgery
		Chronic seizures or epilepsy	Increases risk of seizure	Avoid using during the perioperative period or discretion according to the specialist situation
		Parkinson disease	Worsens parkinsonian symptoms	Use with caution during the perioperative period
21	TCAs (Amitriptyline / doxepin/imipramine etc.)	——	May increase risk of arrhythmia in combination with some volatile anesthetics or sympathomimetics; increases the sedation effect during operation	Gradually stop before surgery or discretion according to the specialist situation
22	Amitriptyline	General anesthesia	Increases risk of postural hypotension	1.Closely monitor blood pressure during the surgery 2.Use with caution after surgery
23	Fluoxetine, sertraline, citalopram, fluvoxamine	High bleeding risk surgery	Increases risk of bleeding	Stop ≤5 half-life before surgery
		Lower risk of bleeding was assessed	Increases risk of bleeding	Use with caution during the perioperative period
24	Fluoxetine	——	Nervous system adverse reactions (insomnia, dizziness, unconsciousness, upset and agitation)	Pay attention to the symptoms of the nervous system
25	Fluvoxamine	——	Nausea, vomiting and anticholinergic adverse reactions	Pay attention to closely monitoring
26	Paroxetine	——	Increases the sedation effect during operation; increases risk of bleeding	Stop before surgery or discretion according to the specialist situation
		Hypoproteinemia (ALB ≤25g/L)	High protein binding rate, may compete with intraoperative drugs (such as: methylprednisolone 77%, propofol 98%, bupivacaine 95%, midazolam 96%-98%, parecoxib sodium 98%, sufentanil 92.5%) for binding to albumin	Pay attention to adjusting dosage of intraoperative medications with high protein binding rates
		MAOI (Linezolid, methylene blue)	Increases risk of 5-HT syndrome	Cannot be used within 2w before and after using MAOI
27	Duloxetine	——	Increases risk of bleeding due to inhibition of platelet aggregation	Use with caution during the perioperative period, pay attention to the symptoms of bleeding
		Ccr <30ml/min	Increases risk of nausea and vomiting	Avoid using

APPENDIX A (part 3 of 8). The list of high-risk perioperative medications for older patients in China

	Medications or Medication Classes	*Conditions*	*Potential Risks*	*Recommendations*
28	MAOIs: selegiline etc.	——	Increases risk of hypertension, hyperthermia, convulsions and coma	Stop 2w before surgery or discretion according to the specialist situation
		Sympathomimetic (dopamine, ephedrine, phenylephrine)	Increases risk of hypertensive crisis	Avoid using together
		Meperidine	Increases risk of 5-HT syndrome	Avoid using together
29	Lithium	——	Increases risk of arrhythmia and renal diabetes insipidus; prolongs action of neuromuscular blockers	1.Stop 24h before minor surgery 2.Stop 48h before major surgery 3.Pay attention to monitoring electrolyte levels
			Cardiovascular System Medications	
30	Beta blockers: propranolol / metoprolol / atenolol / bisoprolol	——	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
31	Nifedipine, immediate release	——	Increases risk of hypotension and precipitation myocardial ischemia	Consider changing to other CCBs before surgery
32	CCB (except nifedipine, immediate release)	Non-cardiac surgery: vasospasm angina	Withdrawal increases the risk of unstable intraoperative circulatory function	Continue to use on the day of surgery, closely monitor
33	ACEI/ARB	——	Increases the risk of kidney damage	Use other drugs that aggravate kidney damage with caution during the surgery
		Cardiac surgery	Increases risk of perioperative hypotension and vasodilation shock	Stop 1d before or on the day of surgery, depending on the drug
		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
34	ACEI: Captopril / fosinopril / enalapril / benazepril, etc.	Triamterene, amiloride	Increases risk of hyperkalemia	Avoid using amiloride or triamterene (except patients with hypokalemia)
		Spironolactone	Increases risk of hyperkalemia	Monitoring potassium level
35	α1 receptor antagonist: prazosin / doxazosin / terazosin	Cataract surgery	Increases the risk of soft iris syndrome	Stop before surgery
		General anesthesia	Increases risk of postural hypotension and bradycardia	1.Closely monitor blood pressure during the surgery 2.Use with caution after surgery
36	Reserpine	——	Increases the risk of refractory hypotension during the surgery	Stop 1-2w before surgery, for emergency/limited surgery, prepare for norepinephrine
37	Hydrazine, minoxidil	——	Affects intraoperative blood pressure	Stop on the day of surgery
38	Amiodarone	——	Severe arrhythmia (QT interval prolongation and torsades de pointes); Withdrawal cannot control arrhythmia symptoms	Closely monitor ECG
		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

APPENDIX A (part 4 of 8). The list of high-risk perioperative medications for older patients in China

	Medications or Medication Classes	*Conditions*	*Potential Risks*	*Recommendations*
39	Isosorbide dinitrate, isosorbide mononitrate	——	Continued using helps control blood pressure and angina, but affects intraoperative blood pressure	Continue to use, pay attention to monitoring intraoperative blood pressure
40	Digoxin > 0.125mg/d	——	Arrhythmia	Use with caution, pay attention to monitoring the concentration of digoxin and potassium level
41	Bile acid sequestrant: cholestyramine	——	Interferes with the absorption of other drugs during the perioperative period	Stop 1d before surgery or on the day of surgery
42	Fibrates	——	Increases risk of rhabdomyolysis	Stop 1d before surgery or on the day of surgery
43	Niacin	——	Risk of vasodilation and itching	Stop 1d before surgery or on the day of surgery
			Respiratory Medications	
44	Theophylline, 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
			Digestive System Medications	
45	Calcium carbonate, aluminum hydroxide	——	Temporary neutralization of stomach acid and cause additional matter in the stomach	Stop on the day of surgery
46	Ranitidine, famotidine	——	Increases risk of delirium	Comprehensive assessment, use with caution during the perioperative period
47	Cimetidine	——	Multiple drug interactions, increases risk of delirium	Avoid using during the perioperative period
48	Belladonna, scopolamine	——	Increases risk of delirium and cognitive impairment	Use with caution during the perioperative period
49	Metoclopramide, promethazine	Parkinson disease	Worsens parkinsonian symptoms	Use with caution during the perioperative period
50	Laxatives (stimulant, Osmotic, stool softeners)	——	Laxative requirements may change perioperatively due to reduced oral intake or opioid initiation	Stop on the day of surgery
			Urinary System Medications	
51	Thiazines: Hydrochlorothiazide	——	Affects electrolytes and blood volume levels	Continue to use, pay attention to monitoring blood pressure and electrolyte levels
52	Loop diuretics: furosemide / torasemide / bumetanide / ittanic acid	——	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
53	Potassium-sparing diuretics: spironolactone, triamterene	——	Increases risk of hyperkalemia	Stop on the day of surgery or discretion according to the specialist situation, monitor Potassium levels
			Hematological System Medications	
54	Heparin (unfractionated)	——	Increases risk of bleeding	1.Stop 4-6h before surgery if full anticoagulation 2.Restart at least 12h postoperatively if adequate hemostasis 3.Discretion according to the specialist situation

APPENDIX A (part 5 of 8). The list of high-risk perioperative medications for older patients in China

	Medications or Medication Classes	*Conditions*	*Potential Risks*	*Recommendations*
55	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
56	Fondaparinux	——	Increases risk of bleeding	1.Therapeutic: stop 3d before surgery 2.Prophylaxis: stop 48h before surgery
57	Warfarin	Elective surgery	Increases risk of bleeding	Stop 3-5d before surgery, monitor INR (ideally ≤1.5) and bleeding situation
		Emergency surgery	Increases risk of bleeding	Use low-dose oral or sc vitamin K to reduce INR within 24-36h; if emergency, use fresh frozen plasma or prothrombin complex concentrate; monitor bleeding situation
		Surgery with a higher risk of embolization	Increases risk of bleeding	Use bridging therapy with unfractionated or LMWH, monitor bleeding situation
58	Novel oral anticoagulants: dabigatran	Ccr ≤50ml/min and surgery with low bleeding risk	Increases risk of bleeding	Stop at least 1-2d before surgery
		Ccr ≤50ml/min and surgery with low bleeding risk	Increases risk of bleeding	Stop at least 2-3d before surgery
		Ccr ≤50ml/min and surgery with high bleeding risk or spinal/epidural anesthesia	Increases risk of bleeding	Stop at least 2-3d before surgery
		Ccr ≤50ml/min and surgery with high bleeding risk or spinal/epidural anesthesia	Increases risk of bleeding	Stop at least 4d before surgery
59	Oral Xa inhibitors: rivaroxaban, apixaban	Normal renal function and surgery with low bleeding risk	Increases risk of bleeding	Stop at least 1d before surgery
		Impaired renal function and surgery with low bleeding risk	Increases risk of bleeding	Stop at least 2d before surgery
		Normal renal function and surgery with high bleeding risk	Increases risk of bleeding	Stop at least 2d before surgery
		Impaired renal function and surgery with high bleeding risk	Increases risk of bleeding	Stop at least 3d before surgery

APPENDIX A (part 6 of 8). The list of high-risk perioperative medications for older patients in China

	Medications or Medication Classes	*Conditions*	*Potential Risks*	*Recommendations*
60	Aspirin (≤100mg/d)	With an arterial stent	Increases risk of bleeding	Continue to use
		Surgery with high bleeding risk such as intracranial surgery, spinal canal surgery, posterior chamber of eye surgery, certain urologic procedures and cardiovascular surgery	Increases risk of bleeding	Stop 1w before surgery or discretion according to the specialist situation
		Surgery (except for the above types) with low bleeding risk	Increases risk of bleeding	Use with caution and monitor bleeding situation
61	Clopidogrel	——	Increases risk of bleeding	Comprehensive assessment, if you need to stop, stop 5-7d before surgery
62	Prasugrel	——	Increases risk of bleeding	Comprehensive assessment, if you need to stop, stop 7d before surgery
63	Ticagrelor	——	Increases risk of bleeding	Comprehensive assessment, if you need to stop, stop 3-5d before surgery
64	Ticlopidine	——	Increases risk of bleeding, cause adverse reactions in the hematological system, safer and effective alternatives available	Avoid using, comprehensive assessment, if you need to stop, stop 10-14d before surgery
65	Dipyridamole	——	Increases risk of postural hypotension and bleeding	Avoid using
66	Cilostazol	——	Increases risk of bleeding	Comprehensive assessment, if you need to stop, stop 3-5d before surgery
			Endocrine System Medications	
67	Methylprednisolone, dexamethasone, hydrocortisone, prednisolone	——	Withdrawal increases the risk of Addison's crisis	Take the morning dose as usual on the day of surgery, if necessary, add hydrocortisone during surgery
		Use NSAIDs together	Increases risk of bleeding	Monitoring bleeding situation
68	Quick-acting insulin: NovoRapid Short-acting insulin: Insulin Injection, Novolin R, Humulin R	Surgery requiring fasting water	Increases risk of hypoglycemia	Stop on the day of surgery

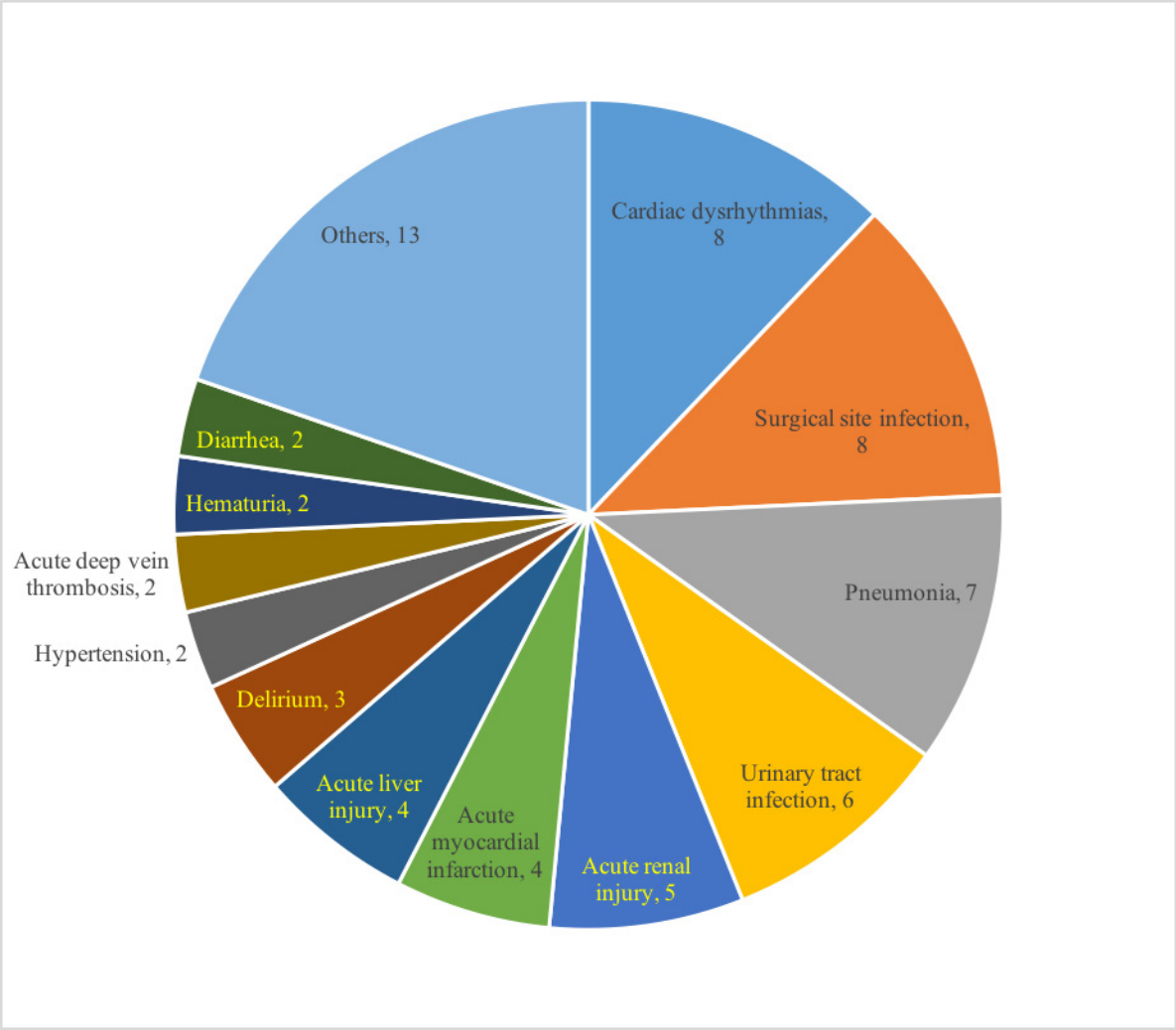
APPENDIX A (part 7 of 8). The list of high-risk perioperative medications for older patients in China

	Medications or Medication Classes	*Conditions*	*Potential Risks*	*Recommendations*
69	Metformin	Can eat or drink after surgery	Increases risk of lactic acidosis	Stop on the day of surgery
		Cannot eat or drink within 24 hours after surgery	Increases risk of lactic acidosis	Stop 48h before surgery
		Renal insufficiency, intraoperative venous contrast or general anesthesia	Increases risk of lactic acidosis	1.Stop 48h before surgery 2.Monitor renal function after 2-3 days of radiography and restart after normal results
		Normal renal function and intraoperative venous contrast	Increases risk of lactic acidosis	1.Stop on the day of surgery 2.Monitor renal function after 2-3 days of radiography and restart after normal results
70	Sulfonylureas: glimepiride, glibenclamide, gliclazone, glipizide, gliclazide etc.	Surgery requiring fasting water	Increases risk of hypoglycemia	Stop on the day of surgery
71	Non-sulfonylureas: nateglinide, repaglinide	Surgery requiring fasting water	Increases risk of hypoglycemia	Stop on the day of surgery
72	Thiazolidinediones: pioglitazone	——	Increases risk of hypoglycemia and postoperative fluid retention	Stop on the day of surgery
73	Bisphosphonates: alendronate	——	Increases risk of esophageal ulcers	Stop at least 1d before surgery and restart after patients can correctly use it
74	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
			Anti-Infective Medications	
75	Vancomycin, aminoglycosides	——	Increases risk of kidney damage	Monitor renal function
			Antipyretic, Analgesic, Anti-Inflammatory And Anti-Rheumatic Medications	
76	NSAIDs: Aspirin>325 mg/d, ibuprofen, indomethacin, diclofenac, naproxen	——	Increases risk of bleeding and kidney damage	1.Comprehensive assessment, use with caution, pay attention to monitoring. If you need to stop, according to the half-life of drug. Short-acting (ibuprofen / indomethacin / diclofenac) stopped 1d pre-op, long-acting (naproxen) stopped 4d pre-op 2.Use drugs that aggravate kidney damage with caution during the surgery
		Major orthopedic surgery	Increases risk of bleeding and kidney damage	Stop 4-7d before surgery or discretion according to the specialist situation
		Age>75; taking oral or parenteral corticosteroids, anticoagulants, antiplatelet agents, antidepressants or drugs with high protein binding rates	Increases risk of upper gastrointestinal ulcers and gross bleeding (occur in approximately 1% of patients treated for 3–6 months and in ~2–4% of patients treated for 1 year)	Pay attention to monitoring and can use PPI/H2R for prevention

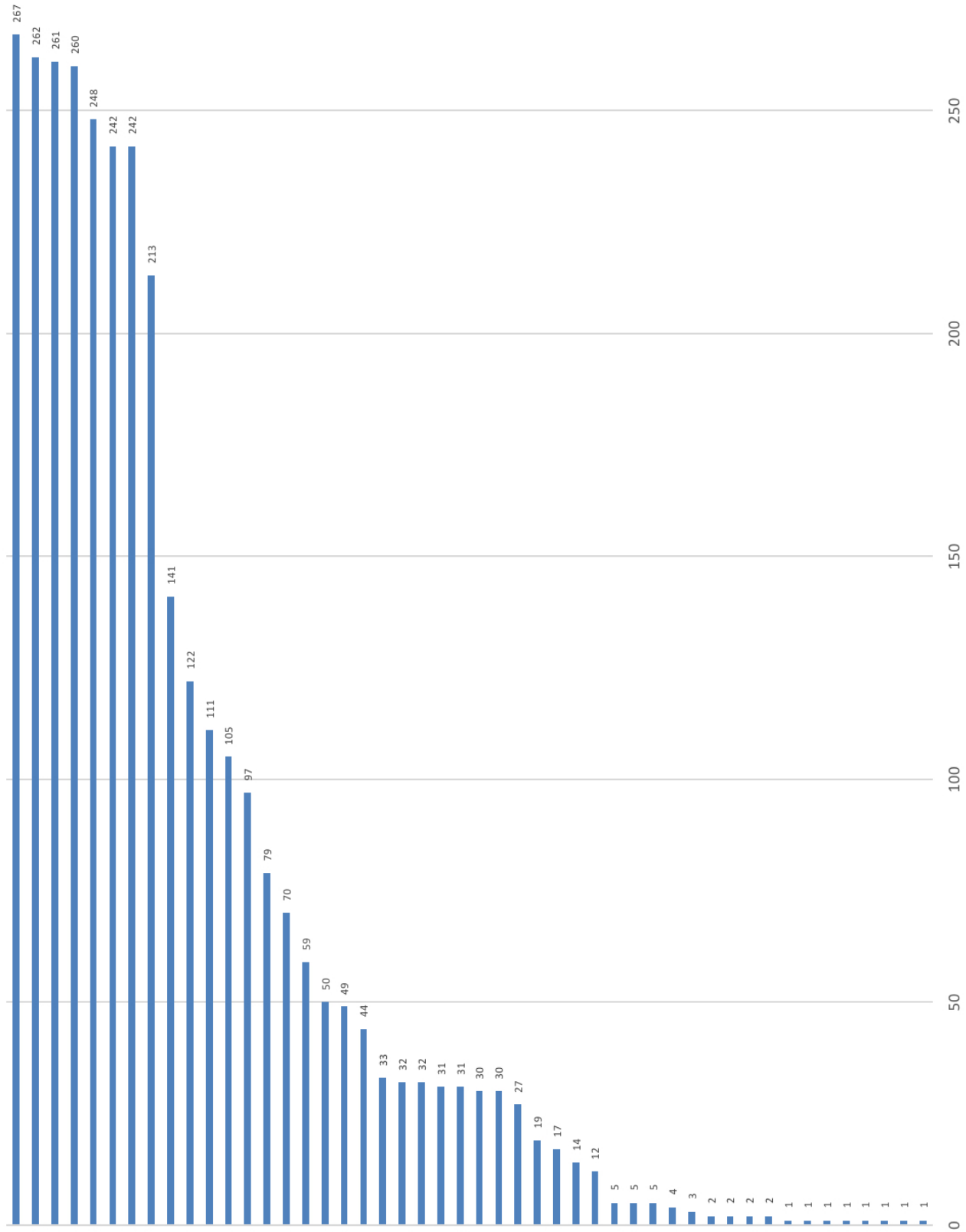
APPENDIX A (part 8 of 8). The list of high-risk perioperative medications for older patients in China

	Medications or Medication Classes	*Conditions*	*Potential Risks*	*Recommendations*
77	Indometacin	——	More neurologic adverse reactions than other NSAIDs	Consider changing to other NASIDs
78	Cox2 inhibitors: celecoxib, meloxicam	——	Affects renal function	Continue to use for patients with normal renal function, pay attention to monitoring renal function during the perioperative period
79	NSAIDs	Renal insufficiency	Retention of water and sodium, can aggravate or cause kidney failure	Avoid using during the perioperative period
80	Leflunomide	——	Continued using has the risk of bone marrow and immunosuppression	Stop 2w before surgery and restart after wound healing
81	Methotrexate	——	Hinders wound healing, increases risk of bone marrow, immunosuppression and kidney damage	Use with caution for patients with normal renal function, if you need to stop, stop 1w before surgery, monitor renal function
82	Azathioprine	——	Major wound complications and increases risk of bone marrow cytotoxicity during the perioperative period	Stop before surgery
			Antiallergic Medications	
83	Chlorpheniramine, cyproheptadine, diphenhydramine (oral), promethazine	——	Increases risk of delirium and potentially enhances the sedative effect of general anesthetics	Stop 1d before surgery
			Other Medications	
84	Rituximab, etanercept	——	Potential risk of infection	Depending on the drug, stop at two half-lives or at least one dosing interval before surgery
85	Bevacizumab	——	Risk of affecting wound healing or opening	Stop at least **28d before surgery**
86	Ranibizumab, Conbercept	Ophthalmic surgery	Increases risk of infection and bleeding	Stop 28d before and after surgery

APPENDIX B. Postoperative complications



APPENDIX C. Intraoperative medication (*indicates HRPOMs)



APPENDIX D. Postoperative complications in patients receiving vancomycin

Serial No.	*Sex*	*Age*	*Days of Vancomycin Use*	*Postoperative Complications*
1	Male	78	6	Suspected pulmonary infection
2	Male	84	14	None
3	Female	82	9	None
4	Female	82	4	Infection of surgical incision
5	Male	77	9	Increased risk of infection due to large scope of surgery
6	Female	87	7	Suspected surgical incision infection
7	Male	76	5	Definite pulmonary infection
8	Female	86	2	Suspected pulmonary infection
9	Female	83	16	Increased risk of infection due to large scope of surgery
10	Female	75	6	Pulmonary infection
11	Female	80	5	Suspected pulmonary infection
12	Female	80	2	Infection of surgical incision
13	Male	81	5	Suspected surgical incision infection
14	Male	80	9	Infection of surgical incision
15	Male	77	2	None
16	Female	77	12	Increased risk of infection due to large scope of surgery
17	Male	82	2	Definite pulmonary infection
18	Male	80	14	Increased risk of infection due to large scope of surgery
19	Male	87	9	Infection of surgical incision
20	Female	75	3	None
21	Female	78	3	Suspected surgical incision infection
22	Male	76	6	Increased risk of infection due to large scope of surgery
23	Female	77	11	None
24	Male	86	3	Definite pulmonary infection
25	Female	76	3	Definite pulmonary infection