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ORIGINAL RESEARCH

Risk Factors for Non-Adherence to Medications That Affect Surgery: A Retrospective Study in Japan

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Purpose: Data on risk factors for non-adherence to doctors' and pharmacists' instructions to discontinue medications prior to surgery are lacking. This study aimed to identify characteristics and risk factors for such non-adherent patients.

Patients and Methods: Data (including patient age, sex, prescription medications, comorbidities, presence of roommate at home, and number of days between receiving instruction and surgery) of 887 patients who used medications affecting surgery at a university hospital from April 2017 to March 2020 were retrospectively evaluated. The primary endpoint was to investigate the rate of non-adherence and to explore independent risk factors for non-adherence (with age categorized as ≥65 [versus <65] years). Secondary endpoints included analysis of limited number of departments subgroup and a sensitivity analysis (with age categorized as ≥75 [versus <75] years) to confirm the robustness of the primary endpoint results. Independent risk factors for non-adherence were identified using logistic regression analysis.

Results: The non-adherence rate was 11.4% (n=101/887), median age (interquartile range) at admission was 73 (70–79) years, and proportion of male patients was 81.2% (n=82). The main analysis adjusted for age ≥65 (versus <65) years showed age as a risk factor for increased non-adherence (adjusted odds ratio: 2.1, 95% confidence interval: 1.09–4.05; p=0.027). However, analyses adjusted for departments (other than urology, gynecology, and breast surgery, with a large sex bias in hospitalized patients) and for age ≥75 (versus <75) years showed no such risk.

Conclusion: Age ≥65 years was associated with a higher risk of non-adherence to medications that should be discontinued before surgery. It is important for doctors and pharmacists to ensure that patients at high risk for non-adherence are aware of the importance of adherence. Our findings may help identify patients at high risk for non-adherence to such medications.

Keywords: general surgery, medication adherence, patient compliance, pharmacists, risk factors

Plain Language Summary

At Kitasato University Hospital, doctors and pharmacists check the medications taken by patients scheduled for surgery prior to admission and instruct them to discontinue any medications that may affect the surgery. However, there are patients who fail to accurately comply with these instructions, and the risk factors for this have not been identified. In this study, we examined the risk factors for patients who failed to comply with the instructions given by their doctors and pharmacists regarding the use of medications that could affect their surgery. Risk factors were examined using a statistical method for identifying risk factors by considering patients' age ≥65 (versus <65) years, sex, presence of dementia, presence of a roommate at home (as opposed to living alone), number of medications to be discontinued before surgery, and number of days between instructions and surgery as risk factors. A total of 887 patients were included in the study, with a non-adherence rate of 11.4% (n=101/887). The results of the statistical analysis indicated that age ≥65 (versus <65) years may be a risk factor for non-adherence to medications that should be discontinued before surgery based on physician/pharmacist instructions. Physicians and pharmacists need to actively improve adherence to surgery-related medications, understand patient factors associated with medication non-adherence, and provide interventions that can avoid non-adherence and help patients fully understand and improve adherence to instructions.

Introduction

Approximately 312.9 million surgeries are performed each year worldwide.[1] Cancellation of surgery is an important factor leading to economic loss for hospitals.[2–4] Such cancellations are burdensome for patients and hospitals and pose a major

problem in terms of patient-hospital trust and medical malpractice. Studies published since 2016 have reported regional variations in the elective day-of-surgery cancellation rates, ranging from 5% at pediatric ambulatory surgery centers in the United States (US) to 44.5% at general hospitals in South Africa.[5,6] The average cost of a canceled surgery in the US is approximately 4802 US dollars.[3] Non-adherence to surgery-related medications can lead to cancellation of surgery. A systematic review has reported that the main causes of surgery cancellations were hospital-related causes, such as improper scheduling, and patient-related causes, such as patient refusal.[7] In Japan, 19 cases of medical accidents involving the continued administration of medications that were supposed to be withdrawn before a hematological procedure were reported between 2010 and 2015, including three that could have resulted in patient disability.[8] Perioperative bleeding is recognized as a major risk factor for subsequent mortality. A systematic review, evaluating the efficacy and safety of novel oral anticoagulants versus warfarin therapy, found that perioperative administration of novel anticoagulants carried the same risk of major bleeding as warfarin, except in patients undergoing noncardiac surgery, in whom it may be more beneficial.[9] However, to the best of our knowledge, the association between cancellation of surgery and failure to discontinue medications that should have been discontinued before surgery has not been investigated to date.

Verifying the medications used by patients before surgery is one of the most important responsibilities of pharmacists. At Kitasato University Hospital, pharmacists have been checking patients' medications before surgery to ensure appropriate perioperative medication management since September 2013. For patients receiving anticoagulants or other medications that may affect surgery, doctors and pharmacists jointly instruct the patients, in advance, when to discontinue the medications. However, there have been cases wherein patients have been admitted to the hospital without discontinuing their medications that could affect surgery, despite being instructed to discontinue the medications before admission, resulting in cancellation of surgery. There is a need for preoperative optimization strategies, such as discontinuation of anticoagulants used by patients, to improve preoperative cost-effectiveness.[10] A systematic review has reported the effectiveness of preoperative medical consultation by internists in preventing surgery cancellation.[11] Although several studies have reported the causes of patient non-adherence,[12–14] to the best of our knowledge, no study has reported non-adherence related to discontinued medications before surgery. Moreover, the risk factors for non-adherence have not been examined, even when instructions are provided by pharmacists regarding which anticoagulants to discontinue before surgery. Identification of risk factors for non-adherence may help in reducing the burden on patients and financial burden on hospitals associated with canceled surgeries.

Therefore, this study aimed to determine the rate of non-adherence and its risk factors for Asian patients who failed to adhere to the pharmacists' preoperative instructions for discontinuing medications before surgery.

Materials and Methods
Study Design
This retrospective study (level of evidence: III) was conducted at Kitasato University Hospital in Kanagawa, Japan, between April 1, 2017, and March 31, 2020. The hospital is a 1200-bed university hospital that provides tertiary care in Japan. We retrospectively collected data on age, sex, race, medical history, presence of roommate at home (as opposed to living alone), medications, number of days between receiving a pharmacist's explanation and surgery, and department from electronic medical records after July 2021. All collected data were anonymized. Two researchers (YN and AA) independently reviewed the data to confirm data accuracy. Disagreements between researchers were resolved through discussion and, when necessary, consultation with a third senior researcher (AT).

Patients and Eligibility Criteria
Patients were included if they were instructed by their doctors and pharmacists before surgery to discontinue or continue a medication that could affect surgery. The medications that could affect surgery included those (i) with antiplatelet effects, (ii) with anticoagulant effects, (iii) that inhibited coagulation factor X activity, (iv) that inhibited thrombin formation, (v) that improved cerebral blood circulation, and (vi) that improved coronary blood flow. Table S1 lists the medications that could affect surgery and approximate duration (days) of medication discontinuation required before surgery, examinations, and biopsies.

Before admission for surgery (urology, gastrointestinal, otolaryngology, plastic surgery, breast surgery, gynecology, and respiratory surgery), all the patients had their medications checked by a pharmacist. The following patients were excluded from the study: those (i) who were finally instructed by a non-pharmacist, such as doctors or other medical staff, on when to discontinue or to continue medications that would affect their surgery; (ii) whose surgery was postponed or canceled after the pharmacist had provided instructions; (iii) who were using medications that a doctor had instructed to be discontinued other than the medications defined by Kitasato University Hospital to be discontinued before surgery; and (iv) with unknown dates of discontinuation of medications that affect surgery. For patients who had more than two surgical procedures during the study period, the most recent data were used.

By definition, in this study, surgery included examinations and biopsies in addition to surgeries performed after a scheduled hospitalization and included procedures in which bleeding could have been affected if certain drugs were continued before the surgery. The examinations for which pharmacist interviews were conducted were agreed upon in advance between each department and the pharmacy department.

Protocol After Surgical Decision

A doctor confirmed the medications to be used by patients who were to undergo surgery during the consultation, orally explained to the patients whether the medication should be discontinued or continued, and recorded the explanation in the electronic medical records. The pharmacist interviewed the patients after the doctor's consultation, checked the medications being used and the doctor's record of instructions, and explained orally and in writing whether the medication should be discontinued or continued. In principle, the instructions from the doctor and pharmacist to discontinue a medication covered medications that would affect the surgery; therefore, those that were not included, were continued. If there was an error in the doctor's record, the pharmacist called the doctor to confirm the details of the instruction and explained the correct information again to the patient. Then, the pharmacist recorded the instruction given to the patient in the electronic medical records. The interviewing pharmacists were trained by senior pharmacists to ensure uniformity of briefing to all the pharmacists. Patients were asked to discontinue any medication that needed to be discontinued before admission or at the time when the patient was instructed by the doctor and pharmacist. If the date of surgery could not be determined at the end of the doctor's consultation, the doctor and pharmacist explained only the approximate date when the patient should discontinue taking the medication that can affect surgery. Once the surgery date was confirmed, a non-pharmacist (other doctors or medical staff requested by the doctor) called the patient on the telephone to orally instruct the date of discontinuation of the medication that affects surgery.

Non-Adherence Definition

In this study, non-adherence was defined as not following the instructions as explained by the doctors and pharmacists preoperatively, when admitted. The main cutoff point between non-adherence and adherence was whether the patient had discontinued the use of medications affecting surgery on the date instructed by the doctor and pharmacist before admission. Patients were defined as non-adherent by the doctor and pharmacist if they had failed to follow the instructions, for example, discontinued the medication on a date other than the instructed date or discontinued a drug that did not need to be discontinued. On the first day of each patient's admission, the ward pharmacist confirmed by checking the electronic medical record for evidence of adherence to the doctors' and pharmacists' instructions for medication discontinuation. Moreover, the pharmacist in each ward always cross-checked the medications and their usage with the patient and recorded them in the electronic medical record, which was then reviewed by the doctor. Then, the patients were divided into the "adherence" or "non-adherence" group based on whether they followed or did not follow the preoperative instructions, respectively, provided by the doctors and pharmacists at the time of admission.

Sample Size

We used standard methods to calculate the sample size needed for multiple logistic regression analysis, including at least 10 outcomes needed for each independent variable included in the analysis. We assumed a non-adherence rate of 8% and a dropout rate of 50%; therefore, we needed 1750 patients (70 in the non-adherence group) to conduct multiple logistic regression analysis appropriately with six variables.

Statistical Analyses

The primary outcome of the study was an exploration of risk factors for non-adherence. Multivariable logistic regression models were used to examine the effect of independent variables on non-adherence. The risk factors assumed in this study for the primary outcome were as follows: (i) age at the time of hospitalization (≥65 or <65 years), (ii) sex, (iii) presence of dementia, (iv) whether or not a roommate was present at home, (v) number of medications to be discontinued (one, two, and three or more), and (vi) number of days from receipt of instructions from the pharmacist until surgery (≥30 or <30 days). The independent variables were selected based on previous literature or as clinically relevant variables.[12,15–22] Given that the proportion of patients aged ≥65 years is expected to increase in Japan[23] and that age is a risk factor for non-adherence,[20] we used age as a categorical variable with a threshold of 65 years. We used Fisher's exact test and chi-squared test (with the Yates correction) to compare the categorical variables between the adherence and non-adherence groups. The Mann–Whitney U-test was used to analyze continuous variables. Quantitative data are expressed as medians, and categorical data are expressed as absolute values and percentages. Patients with missing data on the study variables were excluded from the univariate and multivariate analyses. However, if the missing data accounted for ≥5%, we planned multiple imputation by chained equations to create 100 sets of multiple imputation data. All statistical analyses were performed using the EZR version 1.36 software (Saitama Medical Center, Jichi Medical University, Saitama, Japan). We also used a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), which is a modified version of R commander designed to add statistical functions frequently used in biostatistics.[24] All tests were two-tailed. A p-value <0.05 was considered statistically significant. As sample size calculation was not performed for subgroup and sensitivity analyses, and p-values other than those for the primary outcome were considered nominal p-values to account for multiplicity.

Subgroup Analysis

Subgroup analysis was performed to test for the robustness of the primary endpoint using a logistic regression model. In the analysis, hospitalized patients in the urology department (which has a large number of male patients) as well as gynecology and breast surgery departments (which have a large number of female patients) were excluded. Due to the small sample size, we set the risk factors as follows: (i) age at the time of hospitalization (≥65 or <65 years), (ii) sex, (iii) presence of dementia, and (iv) whether the patient had a roommate at home.

Sensitivity Analysis

We also conducted a sensitivity analysis to explore the effect of age on the primary outcome using a logistic regression model. We set the risk factors as follows: (i) age at the time of hospitalization (≥75 or <75 years), (ii) sex, (iii) presence of dementia, (iv) whether a roommate was present, (v) number of medications to be discontinued (one, two, and three or more), and (vi) number of days between receiving instructions to discontinue medications from the pharmacist and surgery (≥30 or <30 days). Given that the proportion of patients aged ≥75 years is expected to increase in Japan[23] and that older age is a risk factor for non-adherence,[20] we used age as a categorical variable with a threshold of 75 years to confirm the effect of age.

Results

Patient Characteristics

Of 1529 patients whose clinical data were collected during the study period, 887 (58%) were included in this study (Figure 1). Table 1 shows the baseline patient characteristics. The overall median age was 73 (range: 67–78) years, and 648 (73.1%) patients were men. The rate of non-adherence to the pharmacists' instructions at admission was 11.4% (n=101); of these, the rates of surgery cancellation and change in surgical procedure were 1.0% (n=1) each. There was a significant difference in age group (p=0.046), number of medications (p=0.03), and type of medication that affects surgery (p=0.015) between the adherence and non-adherence groups. Meanwhile, some categorical variables (rate of dementia, presence of roommate, medications that affect surgery, and days until surgery) were not significantly different between the two groups. Urology had the highest number of patients (n=439; 49.5%), followed by gastrointestinal
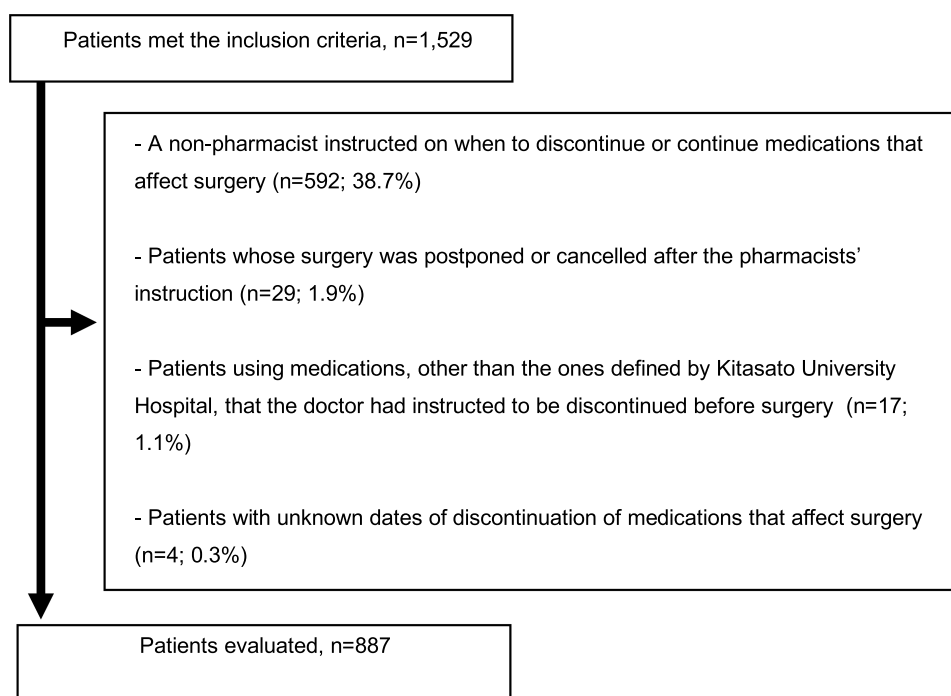
Figure 1 Patient inclusion flowchart.

surgery (n=159; 17.9%) and otolaryngology (n=129; 14.5%). As there were no variables with missing values accounting for ≥5%, multiple imputation was not conducted.

Overall, 5.4% (n=48) and 2.3% (n=20) of the patients discontinued medications that affected surgery earlier or later than when the pharmacists' instructions were given, respectively. In addition, 0.79% (n=7) of the patients discontinued medications on different dates, whereas 1.47% (n=13), 0.23% (n=2), and 1.47% (n=13) discontinued medications other

Table 1 Baseline Patient Characteristics

Characteristics	Total (n=887)	Adherence Group (n=786)	Non-Adherence Group (n=101)	p-value
Age				
Median (IQR), years	73 (67–78)	73 (67–78)	73 (70–79)	0.200
Age group, n (%)				
≤64 years	176 (19.8)	165 (21)	11 (10.9)	0.046*
65–74 years	326 (36.8)	282 (35.9)	44 (43.6)	
≥75 years	385 (43.4)	339 (43.1)	46 (45.5)	
Sex, n (%)				
Male	648 (73.1)	566 (72.0)	82 (81.2)	0.066
Female	239 (26.9)	220 (28.0)	19 (18.8)	
Race, n (%)				
Asian	885 (99.9)	784 (99.8)	101 (100.0)	1.000

(*Continued*)

Table 1 (Continued).

Characteristics	Total (n=887)	Adherence Group (n=786)	Non-Adherence Group (n=101)	p-value
White	1 (0.1)	1 (0.1)	0 (0.0)	
Missing data	1 (0.1)	1 (0.1)	0 (0.0)	
Presence of dementia, n (%)	16 (1.9)	12 (1.6)	4 (4.1)	0.181
Missing data	25 (2.8)	22 (2.8)	3 (3.0)	
Presence of roommate, n (%)	687 (77.5)	612 (80.0)	75 (76.5)	0.503
Missing data	24 (2.7)	21 (2.7)	3 (3.0)	
Number of medications				
Median (IQR)	7 (5–10)	7 (5–10)	6 (4–9)	0.030*
Medications that affect surgery, n (%)				
One	693 (78.1)	617 (78.5)	76 (75.2)	0.735
Two	166 (18.7)	145 (18.4)	21 (20.8)	
Three or more	28 (3.2)	24 (3.1)	4 (4.0)	
Type of medication, n (%)				
Antiplatelet medication	820 (74.9)	719 (74.3)	101 (79.5)	0.015*
Anticoagulant medication	81 (7.4)	80 (8.3)	1 (0.8)	
Activated coagulation factor X inhibitor	131 (12.0)	114 (11.8)	17 (13.3)	
Thrombin inhibitor	23 (2.1)	21 (2.2)	2 (1.6)	
Improve cerebral blood circulation	12 (1.1)	10 (1.0)	2 (1.6)	
Improve coronary blood flow	28 (2.6)	24 (2.4)	4 (3.2)	
Number of days until surgery				
Median (IQR), days	17 (11–26)	16 (11–26)	20 (14–27)	0.084
n (%)				
<30	761 (85.8)	674 (85.8)	87 (86.1)	1.000
≥30	126 (14.2)	112 (14.2)	14 (13.9)	
Department, n (%)				
Urology	439 (49.5)	382 (48.6)	57 (56.4)	0.318
Gastrointestinal surgery	159 (17.9)	144 (18.3)	15 (14.9)	
Otolaryngology	129 (14.5)	113 (14.4)	16 (15.8)	
Plastic surgery	95 (10.7)	89 (11.3)	6 (5.9)	
Gynecology	34 (3.8)	32 (4.1)	2 (2.0)	
Breast surgery	22 (2.5)	19 (2.4)	3 (3.0)	
Respiratory surgery	9 (1.0)	7 (0.9)	2 (2.0)	

Notes: *Significant (p<0.05). p-values for continuous variables (age, number of medications, number of days until surgery) were calculated using the Mann–Whitney U-test. Those for categorical variables (age group, number of days until surgery, sex, presence of roommate, and type of medication) were calculated using chi-squared test. For other categorical variables (race, medications that affect surgery, type of medication, department), p-values were calculated using Fisher's exact test.
Abbreviation: IQR, interquartile range.

than those that affected surgery, discontinued all medications at their own discretion, and discontinued medications that affected surgery but should not be discontinued, respectively.

Primary Outcome

Multivariate logistic regression analysis showed that age ($\geq$65 years) was an independent risk factor for non-adherence to medication (adjusted odds ratio: 2.1, 95% confidence interval: 1.09–4.05; p=0.027) before surgery (Table 2).

Subgroup Analysis Results

Multivariate logistic regression analysis, performed excluding urology, gynecology, and breast surgery inpatients, showed no independent risk factors (Table 3).

Sensitivity Analysis Results

Table 4 shows the results of the sensitivity analysis to identify independent risk factors for non-adherence to medications that affect surgery. There was no risk factor for non-adherence to medication. The results after adjusting for age ($\geq$75 years) in the sensitivity analysis confirmed the findings that differed from those of the primary analysis.

Table 2 Multivariate Logistic Regression Analysis of Risk Factors for Medication Non-Adherence That Affect Surgery (n=887)

Risk Factor	Odds Ratio (95% CI)	p-value
Age		
<65 years	1 (ref)	
≥65 years	2.1 (1.09–4.05)	0.027*
Sex		
Male	1 (ref)	
Female	0.63 (0.37–1.08)	0.091
Presence of dementia		
No	1 (ref)	
Yes	2.49 (0.78–7.94)	0.12
Presence of roommate		
No	1 (ref)	
Yes	0.78 (0.47–1.29)	0.34
Medications		
One	1 (ref)	
Two	1.0 (0.59–1.73)	0.99
Three or more	1.26 (0.42–3.77)	0.67
Days until surgery		
<30	1 (ref)	
≥30	1.13 (0.61–2.08)	0.70

Note: *Significant (p<0.05).
Abbreviations: CI, confidence interval; ref, reference.

Table 3 Multivariate Logistic Regression Analysis of Risk Factors for Medication Non-Adherence That Affects Surgery, Adjusted for Departmental Effects (n=392)

Risk Factor	Odds Ratio (95% CI)	p-value
Age		
<65 years	1 (ref)	
≥65 years	1.63 (0.61–4.36)	0.33
Sex		
Male	1 (ref)	
Female	0.83 (0.40–1.69)	0.6
Presence of dementia		
No	1 (ref)	
Yes	1.49 (0.17–12.90)	0.72
Presence of roommate		
No	1 (ref)	
Yes	0.58 (0.28–1.21)	0.15

Abbreviations: CI, confidence interval; ref, reference.

Table 4 Multivariate Logistic Regression Analysis of Risk Factors for Medication Non-Adherence That Affects Surgery, Adjusted for Age (n=887)

Risk factor	Odds ratio (95% CI)	p-value
Age		
<75 years	1 (ref)	
≥75 years	1.05 (0.69–1.62)	0.81
Sex		
Male	1 (ref)	
Female	0.62 (0.36–1.05)	0.074
Presence of dementia		
No	1 (ref)	
Yes	2.54 (0.79–8.11)	0.12
Presence of roommate		
No	1 (ref)	
Yes	0.79 (0.48–1.30)	0.35
Medications that affect surgery		
One	1 (ref)	
Two	1.02 (0.60–1.75)	0.94
Three or more	1.23 (0.41–3.67)	0.71

(*Continued*)

Table 4 (Continued).

Risk factor	Odds ratio (95% CI)	p-value
Days until surgery		
<30	1 (ref)	
≥30	1.04 (0.56–1.91)	0.9

Abbreviations: CI, confidence interval; ref, reference.

Discussion

In this study, we examined risk factors for non-adherence to medication in patients who were instructed by their doctors and pharmacists to discontinue medications that affect surgery, using multivariate logistic regression analysis after adjustment for patients' clinical characteristics and the number of days between the instructions and the surgery. The results of this study revealed differences between the adherence and non-adherence groups in terms of the age group, number of medications used at the time of admission (categorized), and types of medications that affect surgery (categorized). Multivariate logistic regression analysis was performed to analyze the risk factors for non-adherence to medication, and age ≥65 years was identified as a risk factor for non-adherence. On the other hand, the sensitivity analysis after adjustment for age showed that age ≥75 years was not a risk factor for non-adherence. In a subgroup analysis of risk factors for non-adherence adjusted for departments except urology, gynecology, and breast surgery, no clinical risk factors were identified.

A systematic review has reported the effectiveness of preoperative consultation by internists to prevent surgery cancellation.[11] However, for medications that affect surgery, data that clearly indicate the risk factors for non-adherence to prior instructions are lacking. Previous systematic reviews have reported different risk factors for non-adherence due to differences in the definition of target diseases and therapeutic medications.[12,16,18,25] Age, sex, dementia, and presence of a roommate have been reported as risk factors for non-adherence.[12,18,21] In our study, we newly analyzed the number of medications to be discontinued before surgery and the number of days between the pharmacist interview and surgery as risk factors for non-adherence. A meta-analysis of risk factors for non-adherence in patients with Parkinson's disease suggested that young age was associated with non-adherence.[18] However, according to a meta-analysis of risk factors for non-adherence to lipid-lowering medications, 10 of 11 studies found that adherence and age had a U-shaped association,[19] and an Asian nationwide study revealed the same relation.[20] Although the results of this study do not support those of previous research, they suggest that age ≥65 years in patients may be a risk factor for non-adherence compared with age <65 years (Tables 2 and S2). However, considering the results of previous studies[19,20] and results of the sensitivity analysis in our study (Table 4), older age is not a risk factor for non-adherence. Furthermore, the sensitivity analysis did not take multiplicity into account; therefore, care should be taken when generalizing our results. In the future, it is necessary to clarify the relationship between age group and non-adherence, which was not clarified in this study.

This study also examined the relationship between sex and non-adherence. A systematic review of 25 risk factors for medication non-adherence in 12,603 adult hypertensive patients reported that the risk was higher in men.[12] On the other hand, a systematic review of six studies on medication non-adherence in 8147 patients with Crohn's disease and rheumatoid arthritis reported a higher risk in women.[16] Women tended to have lower odds ratios for non-adherence in the present study, suggesting that being female is a risk factor for non-adherence; however, sex was not significantly associated with non-adherence in the main analysis (Tables 2–4). The reason for these results may be that 49.5% of the patients in this study were urology inpatients, and overall, 73.1% were men. Therefore, there may have been a sex bias (Table 1). The proportion of eligible patients was higher among those undergoing urology surgery because more examinations and biopsies that caused bleeding were performed. In addition, patients from seven departments were included in the study, and selection bias may have occurred because the proportion and characteristics of patients in each department differed. Therefore, future analysis of risk factors for non-adherence to medications that affect surgery should be conducted for each department. In the subgroup analysis of this study, risk factors for non-adherence were examined, except for departments with a large sex bias in the patients studied, although no factors were found to be

significant. A possible reason for this result is the low power due to the small number of patients included in the subgroup analysis. Further studies with large sample sizes are needed to elucidate the association between sex and non-adherence.

This study also examined the relationship between dementia and non-adherence. A systematic review of risk factors for non-adherence in patients with dyslipidemia reported that dementia was associated with a higher risk.[15] In this study, the odds ratio for non-adherence was 2.49 times higher in patients with dementia than in those without dementia, but was not significantly associated with non-adherence (Table 2). A possible reason for this result could be the low power of detection due to the small number of patients with dementia, which was 1.9% (n=16) of the total number of patients. This study also examined whether the number of medications to be discontinued before surgery and number of days between receiving a pharmacist's explanation and surgery were risk factors for non-adherence. A systematic review of risk factors for non-adherence to anticoagulants in patients with atrial fibrillation reported that a high number of concomitant medications is associated with a high risk of non-adherence.[17] On the other hand, the relationship between the number of days between the pharmacist's instructions and surgery and non-adherence has not been reported to our knowledge. In this study, neither the number of medications to be discontinued before surgery nor the number of days between receiving a pharmacist's explanation and surgery showed a significant association with non-adherence (Table 2). Possible reasons for this result include the fact that the number of eligible patients decreases with an increase in the number of medications to be discontinued and low power of detection due to the small number of patients who take more than 30 days to discontinue a drug from the time they receive the pharmacist's explanation to the surgery. Further studies with larger sample sizes are needed to clarify the association between these risk factors and non-adherence. In addition, it is necessary to further subdivide the day period between surgeries, which this study was unable to do, to clarify its relationship with non-adherence. In this study, the rates related to surgical discontinuation and change in surgical procedure were 0.1% (n=1) each. To the best of our knowledge, this is the first retrospective study globally to evaluate the risk factors for non-adherence to anticoagulant discontinuation instructed by pharmacists, so we could not compare our results with those of previous studies. A systematic review of non-adherence to antihypertensive medications suggested that Asians have a higher rate of non-adherence than Americans and Europeans.[12] A systematic review reported that pharmacists' interventions improved patients' adherence.[26–28] Furthermore, a systematic review of 29 studies that used text messages to improve adherence found efficacy in interventions that used motivational messages.[29] Therefore, for Asian patients, more aggressive interventions are needed by pharmacists for preoperative discontinuation of medications. In this study, the pharmacists only intervened via one face-to-face interview, and future interventions are needed to improve patient adherence before surgery using text messages or smartphone applications with reminders about medication adherence.[30]

Although age ≥65 years was identified as a risk factor for non-adherence, doctors and pharmacists need to be aware that the mechanisms underlying adherence are complex and probably not solely determined by simple individual patient factors. Interventions tailored to patient characteristics, such as explaining the disadvantages of taking medications that should be discontinued before surgery, using reminders regarding medications that should be discontinued before surgery, and actively involving family members, may be necessary.

The following challenges for future research were considered: (i) consistent categorization of age and other risk factors; (ii) more consistent definition of non-adherence; (iii) ability to distinguish between intentional and unintentional non-adherence; (iv) identification of risk factors including patient education, race, and other risk factors that could not be included in this study; and (iv) evaluation of the impact of non-adherence on hospital economics.

Limitations

The limitations of this study include the non-randomization and statistical analysis of a limited number of risk factors and departments in Asian patients that may contribute to bias. Therefore, our results are not generalizable, although the elucidation of risk factors for non-adherence to discontinuation of medications that affect surgery may allow us to examine measures to improve adherence in the future. Furthermore, the study excluded 592 patients for whom a non-pharmacist instructed on the timing of discontinuation or continuation of medication that could affect the surgery (Figure 1). If these patients had been included, the results may have been different. In the future, we plan to use

propensity score matching to investigate whether patients who were instructed by pharmacists and non-pharmacists differ in non-adherence. The major strength of this study is that to the best of our knowledge, this is the first exploratory study to analyze the risk factors for non-adherence to medications that should be discontinued before surgery, in a large sample of Asian patients.

Conclusions

This study showed that age ≥65 years may be a risk factor for non-adherence to medications that should be discontinued before surgery based on the doctors and pharmacists' instructions. Doctors and pharmacists need to intervene aggressively to improve adherence to surgery-related medications; they should understand the patient factors associated with medication non-adherence to be able to improve non-adherence by implementing interventions that make non-adherence avoidable and by ensuring that the patients fully understand. Finally, it is important that patients at high risk for non-adherence be made aware of the importance of adherence.

Data Sharing Statement

The data that support the findings of this study are openly available in "Dataset Akamine Akihiko3" at https://data.mendeley.com/datasets/xgw4x56b42/1.

Ethics Approval and Informed Consent

The study was approved by the Institutional Review Board for Observation and Epidemiological Study at the University of Kitasato (KMEO B21-013) and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Informed consent was obtained in the form of an opt-out method on the Kitasato University School of Medicine website.

Consent for Publication

We have obtained ethical approval from the Institutional Review Board for Observation and Epidemiological Study at the University of Kitasato (KMEO B21-013) to conduct the research and permission to use the information in the database for research purposes. There were no requests for non-participation by the studied patients in the conduct of this study. We have ensured that all acquired data and patient information have been anonymized.

Acknowledgments

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Disclosure

The authors report no conflicts of interest in this work.

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