Observational Study

Medicine

OPEN

# The importance of renal function in anemic patients treated with edoxaban after orthopedic surgery in a real-world clinical setting

## A retrospective study

Yasuhisa Izushi, PhD[a,b,*], Yoichiro Takami, PhD[c], Soichiro Ushio, PhD[d], Tomonori Tetsunaga, MD, PhD[e], Naofumi Shiota, MD, PhD[f], Hiroshi Yamamoto, BPharm[g], Toru Sato, MD[h], Yoshihisa Kitamura, PhD[a,d]

**Abstract**

Edoxaban (Edx) has been approved to prevent venous thromboembolism after total knee and/or hip arthroplasty in Japan. However, the risk of anemia with Edx treatment remains elusive. No risk factors for Edx-associated anemia after orthopedic surgery have been reported. This study aimed to clarify the risk of anemia associated with Edx treatment and determine the risk factors for Edx-associated anemia after orthopedic surgery with a high risk for bleeding. First, the association between Edx treatment and the incidence of anemia-related events was retrospectively investigated by pharmacovigilance analyses using data from 5769,866 reports between the first quarters of 2016 and 2020 in the Food and Drug Administration Adverse Event Reporting System and 2752,050 reports between the fourth quarters of 2011 and 2019 in the Japanese Adverse Drug Event Report. Second, 221 patients who underwent Edx treatment after total knee and/or hip arthroplasty between July 2011 and June 2012 at a single center were included in a case–control study to clarify the risk factors for anemia. Edx treatment was associated with an increased risk of anemia-related events in orthopedic patients. Reduced renal function was identified as a critical risk factor for Edx-associated anemia after orthopedic surgery. The present study indicates that renal function should be considered in the risk management of increased Edx-associated anemia after orthopedic surgery.

**Abbreviations:** APTT = activated partial thromboplastin time, BMI = body mass index, BW = body weight, CIs = confidence intervals, CrCl = creatinine clearance, Edx = edoxaban, FAERS = food and drug administration adverse event reporting system, Hgb = hemoglobin, JADER = Japanese adverse drug event report, LRF = low renal function, MedDRA = medical dictionary for regulatory activities, NRF = normal renal function, PODs = postoperative days, PT = prothrombin time, PT-INR = prothrombin time-international normalized ratio, PTs = preferred terms, RBC = red blood cell, ROC = receiver operating characteristic, RORs = reporting odds ratios, TKA/THA = total knee arthroplasty/total hip arthroplasty, VIF = variance inflation factor.

**Keywords:** anemia, edoxaban, coagulation parameters, large-scale spontaneous reporting systems, renal function, risk factor

## 1. Introduction

Edoxaban (Edx) is a factor Xa inhibitor administered orally once daily at a fixed dose without routine coagulation monitoring.[1] It has been approved globally for the prevention of thromboembolism.[2,3] In Japan, Edx is also administered to prevent venous thromboembolism after total knee and/or hip arthroplasty (TKA/THA).[4]

However, Edx treatment increased the frequency of anemia after TKA/THA compared with fondaparinux, the primary conventional anticoagulant, at only a single center.[5,6] Therefore, the risk of anemia with Edx treatment remains elusive. Additionally, no information is available regarding the risk factors for anemia before initiating Edx treatment.

The danger of developing anemia after orthopedic surgery can cause an increase in the hospital stay duration and mortality

*The authors have no funding and conflicts of interest to disclose.*

*The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.*

*Supplemental Digital Content is available for this article.*

*[a] Department of Pharmacotherapy, School of Pharmacy, Shujitsu University, Naka-ku, Okayama, Japan, [b] Division of Molecular and Cellular Medicine, Department of Clinical Science, National Hospital Organization Okayama Medical Centre, Okayama, Japan, [c] Pharmaceutical Care and Health Sciences, School of Pharmacy, Shujitsu University, Naka-ku, Okayama, Japan, [d] Department of Pharmacy, Okayama University Hospital, Kita-ku, Okayama, Japan, [e] Department of Orthopaedic Surgery, Okayama University Hospital, Kitaku, Okayama, Japan, [f] Department of Orthopaedic Surgery and Rehabilitation, National Hospital Organization Okayama Medical Centre, Kita-ku, Okayama, Japan, [g] Department of Pharmacy, National Hospital Organization Okayama Medical Centre, Kita-ku, Okayama, Japan, [h] Department of Orthopaedic Surgery, National Hospital Organization Okayama Medical Centre, Kita-ku, Okayama, Japan.*

** Correspondence: Yasuhisa Izushi, Department of Pharmacotherapy, School of Pharmacy, Shujitsu University, 1–6-1 Nishigawara, Naka-ku, Okayama 703–8516, Japan (e-mail: y-izushi@shujitsu.ac.jp).*

*Copyright © 2022 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.*

*How to cite this article: Izushi Y, Takami Y, Ushio S, Tetsunaga T, Shiota N, Yamamoto H, Sato T, Kitamura Y. The importance of renal function in anemic patients treated with edoxaban after orthopedic surgery in a real-world clinical setting: A retrospective study. Medicine 2022;101:47(e31298).*

*Received: 30 March 2022 / Received in final form: 19 September 2022 / Accepted: 20 September 2022*

*http://dx.doi.org/10.1097/MD.0000000000031298*

because of increased adverse effects, such as postoperative bleeding, transfusion, infection, poor wound healing, and delayed recovery of physical function.[7–9]

Therefore, the risk of Edx on anemia must be confirmed and the risk factors for preventing anemia during Edx treatment after surgery must be controlled.

This study aimed to clarify the risk of anemia associated with Edx treatment and determine the risk factors for Edx-associated anemia. First, we determined the association between Edx treatment and anemia-related events by performing pharmacovigilance analyses. Second, we retrospectively identified the risk factors for Edx-associated anemia by analyzing the preoperative background data of patients who underwent TKA/THA at a single center.

This study revealed that Edx treatment has a higher risk of anemia-related events and that lower renal function is a risk factor for anemia during Edx treatment after orthopedic surgery with a high risk of bleeding.

## 2. Methods

### *2.1. Study design*

This study comprised 3 studies. First, the large-scale reporting system databases of the US Food and Drug Administration and pharmaceuticals and medical devices agency were used for pharmacovigilance analysis to assess the risk of anemia.[10,11] Next, the risk factors for anemia in patients who underwent Edx treatment after surgery were retrospectively investigated in a case–control study as the secondary analysis of 2 previous studies.[5,6] Finally, the association of the detected risk factors for anemia with the hemoglobin (Hgb) levels, coagulation parameters, and transfusion during Edx treatment after surgery was investigated.

### *2.2. Setting and participants*

The food and drug administration Adverse Event Reporting System (FAERS) and Japanese Adverse Drug Event Report (JADER) databases were used for pharmacovigilance analysis.[10–12] FAERS database analysis was performed using CzeekV Pro (https://pro.czeek.com/; version 5.0.30), a program used to search for reports within the database. All the reports in the FAERS database from the first quarter of 2016 to the first quarter of 2020 were analyzed. Additionally, all the reports on patients aged ≥ 20 years in the JADER database from the fourth quarter of 2011 to the fourth quarter of 2019 downloaded from the pharmaceuticals and medical devices agency website were analyzed.[11]

Reports on patients with lower limb orthopedic diseases associated with TKA/THA were extracted from the JADER database to assess the risk of anemia in patients undergoing Edx treatment relative to those treated with fondaparinux and warfarin as conventional anticoagulants. Patients with typical lower limb orthopedic disease were screened using appropriately coded preferred terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA, http://www.meddra.org/; version 22.0), as described in detail in the supplementary information 1, http://links.lww.com/MD/H726.

In this retrospective study, 221 patients aged ≥ 20 years who had undergone TKA/THA at the NHO of the Okayama Medical Centre Department of Orthopaedic Surgery from July 2011 to June 2012 were extracted. The exclusion criteria were as follows: administration of blood products for purposes other than transfusion during thromboprophylaxis (5 patients), treatment with anticoagulants other than the study drug (33 patients), different dosages of the study drug (9 patients), renal failure, including those requiring dialysis (5 patients), history of bleeding (1 patient), and inappropriate prescription (1 patient) (Fig. 1). A total of 54 patients were excluded based on the exclusion criteria. The remaining 167 patients who received anticoagulant thromboprophylaxis with oral administration of Edx 30 mg once daily after surgery were evaluated in this retrospective study.

### *2.3. Data collection in the retrospective study*

Changes in Hgb level and coagulation parameters, including prothrombin time (PT), international normalized ratio of prothrombin time (PT-INR), and activated partial thromboplastin time (APTT), were evaluated on preoperative examination (preoperative day) and postoperative days (PODs) 1, 3, 7, 10, and 14 or following discontinuation of treatment after surgery because Edx 30 mg was administered orally once daily for 14

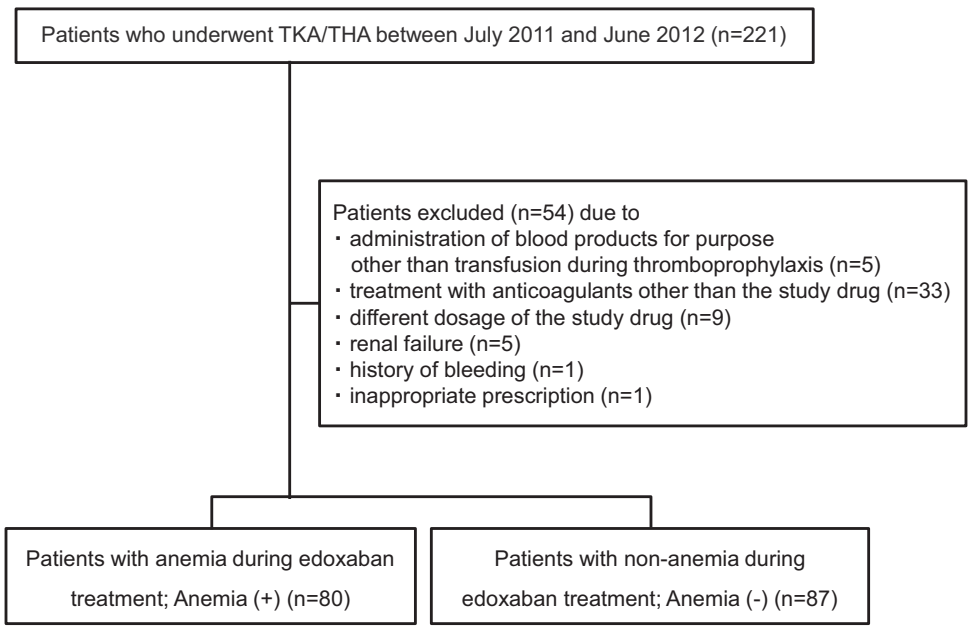


**Figure 1.** Details of the patients included or excluded from the study. THA = total hip arthroplasty, TKA = total knee arthroplasty.

days after surgery (the Japanese standard of care). Additionally, the preoperative characteristics of the patients, such as sex, age, body weight (BW), body mass index (BMI), serum creatinine level, intraoperative hemorrhage volume related to BW, and combined medications, were also investigated as underlying factors. Preoperative renal function was assessed by creatinine clearance (CrCl), which was calculated using the Cockroft-Gault formula. The data were extracted from the medical records and anesthesia information management system under close supervision.

During the study period, the surgical methods and procedures for anesthesia in patients undergoing TKA/THA were standardized. The postoperative care for venous thromboembolism prevention during the study period was also standardized and is described in detail in the supplementary information 2, http://links.lww.com/MD/H727.

### 2.4. Outcome of pharmacovigilance analysis

The primary outcome of the pharmacovigilance analysis was anemia-related adverse events, which were applied to search the databases using the following High-Level Group Terms listed in the MedDRA to extract reports: "Anemias nonhemolytic and marrow depression (10002086)," "Hemoglobinopathies (10018902)," and "Hemolyses and related conditions (10018911)."

### 2.5. Criterion for anemia for the case–control study

In the retrospective analysis, the developed anemia was defined based on the presence of either of the following: a reduction in the Hgb level of at least 2 g/dL or transfusion of at least 2 units of irradiated red blood cell (RBC) concentrate, as previously described.[5,6,13,14] A reduction in the Hgb level of at least 2 g/dL was defined as a decrease from POD 1, as previously described by Sasaki et al[5,6,13] Irradiated RBC concentrates were transfused into patients whose Hgb levels decreased to ≤ 7.5 g/dL or due to symptomatic anemia that had been diagnosed by a clinician.

Because of this criterion for anemia, the 167 patients were divided based on the criterion for anemia to investigate the risk factors for anemia. Accordingly, 80 patients with anemia were eligible for enrollment in the case group [anemia (+)] and 87 patients were eligible for enrollment in the control group [anemia (–)] (Fig. 1).

### 2.6. Ethical matters

This study was approved by the Institutional Review Board of the NHO of the Okayama Medical Centre [approval number 2019–056]. All procedures in this study involving human participants were performed in accordance with the ethical guidelines for medical and health research involving human subjects in Japan and the Helsinki Declaration. Because the present study was retrospective in nature and anonymity was secured, the institutional review board at the NHO Okayama Medical Centre waived the requirement for written informed consent, and an opt-out method was applied by notifications displayed on the hospital's website.

### 2.7. Statistical analyses

All reports from the FAERS and JADER databases were separated into 4 categories: type "a" was defined as anemia-related events with Edx, fondaparinux, or warfarin treatment, type "b" was defined as all other adverse events with each anticoagulant drug, type "c" was defined as anemia-related events with any other drug, and type "d" was defined as all other adverse events with any other drugs. Reporting odds ratios (RORs) were used to detect disproportionality signals of anemia-related events in patients undergoing Edx, fondaparinux, or warfarin treatment relative to all other drugs. RORs were calculated based on 2-by-2 contingency tables of counts using the following formula: (type "a/c")/(type "b/d").[15]

| | Anemia-related events | All other adverse events | Total |
|---|---|---|---|
| Each anticoagulant drug | a | b | a + b |
| All other drugs | c | d | c + d |
| Total | a + c | b + d | a + b + c + d |

$$\mathrm{ROR} = \frac{a/c}{b/d}$$

$$95\%\ \mathrm{CI} = e^{ln(\mathrm{ROR}) \pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$$

The RORs were expressed as point estimates with 95% confidence intervals (95% CIs); ROR values < 1 indicated no potential exposure-event associations, whereas ROR values > 1 indicated the presence of potential exposure-event disproportionality associations. A significant association was detected in

**Table 1A**

**Incidence of anemia in patients undergoing edoxaban treatment based on the JADER and FAERS databases.**

| Database | Drug name | Total | Case | Noncase | ROR | 95% CI | *P* value |
|---|---|---|---|---|---|---|---|
| FAERS | Total | 5769,866 | 64,130 | 5705,736 | | | |
| | Edoxaban | 7031 | 307 | 6724 | 4.08 | 3.64–4.57 | <.001 |
| JADER | Total | 2752,050 | 51,022 | 2701,028 | | | |
| | Edoxaban | 5346 | 308 | 5038 | 3.25 | 2.90–3.65 | <.001 |

CI = confidence interval, FAERS = food and drug administration adverse event reporting system, JADER = Japanese adverse drug event report, ROR = reporting odds ratio.

**Table 1B**

**Incidence of anemia among patients with orthopedic disease based on the JADER database.**

| Drug name | Total | Case | Noncase | ROR | 95% CI | *P* value |
|---|---|---|---|---|---|---|
| Total | 39,695 | 695 | 39,000 | | | |
| Edoxaban | 284 | 21 | 263 | 4.59 | 2.92–7.12 | <.001 |
| Fondaparinux | 82 | 3 | 79 | 2.14 | 0.70–6.06 | .174 |
| Warfarin | 255 | 5 | 250 | 1.12 | 0.49–2.64 | .808 |

CI = confidence interval, JADER = Japanese adverse drug event report, ROR = reporting odds ratio.

the relevant database when the lower limit of the corresponding 95% CI was > 1.

***2.7.1. Retrospective study.*** Continuous variables were expressed as means ± standard deviations or medians. To explore the underlying risk factors that differed between the groups, comparisons were performed using the Mann–Whitney *U* test for continuous variables or Fisher's exact test for categorical variables. Additionally, univariable logistic regression analyses were performed to select significant factors for use in multivariable logistic regression analysis. Multivariable logistic regression analysis was used to obtain the odds ratios for the factors exhibiting the greatest odds ratios in the univariable analyses to identify the risk factors for the development of anemia. Multicollinearity was assessed using the variance inflation factor (VIF). The VIF values did not exceed 10, and the mean VIF was less than 5 in this analysis. The evidence of multicollinearity indicated inconsequential collinearity.[16,17] The correlations between the continuous variables and investigated factors were evaluated using Spearman's correlation coefficient. For each risk factor that exhibited significance in the multivariable logistic regression analysis, the optimal cutoff point of the risk factor for anemia was calculated to optimize sensitivity and specificity. Receiver operating characteristic (ROC) curves were plotted, and the areas under the ROC curve were calculated to determine the optimal threshold for classification accuracy. Continuous variables were analyzed using analysis of variance followed by Tukey's multiple comparison test. Statistical significance was set at $P < .05$ or $P < .01$. All statistical analyses were performed using GraphPad Prism 8.4.0 software (GraphPad Software, Inc., San Diego, CA).

## 3. Results

### 3.1. Disproportionality analysis

***3.1.1. Edx treatment is associated with an increased risk of anemia-related events.*** The 5769,866 reports in the FAERS database included 64,130 cases of anemia-related adverse events (Table 1A). Additionally, the 2752,050 reports in the JADER database included 51,022 cases of anemia-related adverse events (Table 1A). The ROR for anemia-related adverse events with Edx treatment was 4.08 (95% CI: 3.64–4.57; $P < .001$) based on analysis of the FAERS database, while analysis of the JADER database revealed an ROR of 3.25 (95% CI: 2.90–3.65; $P < .001$). In subgroup analysis of the JADER database, 39,695 adverse event reports involving patients with lower limb orthopedic diseases associated with TKA/THA were extracted and included 695 reports focused on anemia-related adverse events (Table 1B). Among these cases, a significant increase in the reporting rate of anemia-related adverse events was detected in patients receiving Edx (ROR, 4.59; 95% CI: 2.92–7.12; $P < .001$). However, for the conventional anticoagulants fondaparinux and warfarin, the ROR for anemia-related events was 2.14 (95% CI: 0.70–6.06; $P = .174$) and 1.12 (95% CI: 0.49–2.64; $P = .808$), respectively.

### 3.2. Retrospective study

***3.2.1. Baseline characteristics of the patients on the preoperative day.*** The baseline characteristics of the 167 patients in this study are shown in Table 2. The patients evaluated in this study were primarily female (81.4%), older (73.2 ± 8.96 years old), and overweight (BMI: 25.5 ± 4.30 kg/m$^2$). These tendencies were the feature of patients with knee or hip osteoarthritis.

***3.2.2. Different preoperative characteristics of patients with anemia compared with those without anemia during Edx treatment.*** The different baseline patient characteristics are also shown in Table 2. Sex, age, BW, BMI, PT, PT-INR, and CrCl differed significantly between the anemia (+) and anemia (-) groups. By contrast, the surgical method, Hgb level, APTT, intraoperative hemorrhage volume, and combined use of antithrombogenic drugs or P-glycoprotein inhibitors did not differ significantly between the groups.

***3.2.3. Evaluation of candidate risk factors for anemia in patients undergoing Edx treatment by univariable logistic regression analysis.*** Based on the results shown in Table 2, the 7 factors that differed significantly between the anemia (+) and anemia (–) groups were evaluated using univariable logistic regression analyses to clarify whether they could be independent preoperative related risk factors for anemia (Table 3A). Anemia was associated with male sex (OR: 2.303; 95% CI: 1.041–5.329; $P = .044$), age (OR: 1.063; 95% CI: 1.024–1.106; $P = .002$), BW (OR: 0.965; 95% CI: 0.938–0.992; $P = .012$), BMI (OR: 0.862; 95% CI: 0.790–0.934; $P < .001$), and CrCl (OR: 0.969; 95% CI: 0.954–0.982; $P < .001$). However, PT and PT-INR were not associated with Edx-associated anemia.

**Table 2**

**Baseline characteristics of the patients before edoxaban treatment (at the preoperative day).**

| Characteristics | Total [n = 167] | Anemia (+) [n = 80] | Anemia (–) [n = 87] | *P* value* |
|---|---|---|---|---|
| Sex (male/female) | 31/136 | 20/60 | 11/76 | .047 |
| Age (yrs) | 73.2 ± 8.96 | 75.5 ± 9.03 | 71.0 ± 8.35 | <.001 |
| Surgical method (TKA/THA) | 108/59 | 57/23 | 51/36 | .106 |
| Body weight (kg) | 59.3 ± 11.9 [n = 161#] | 56.8 ± 11.2 [n = 77#] | 61.6 ± 12.1 [n = 84#] | .013 |
| BMI (kg/m$^2$) | 25.5 ± 4.30 [n = 161#] | 24.2 ± 3.3 [n = 77#] | 26.7 ± 4.7 [n = 84#] | <.001 |
| Hgb (g/dL) | 12.7 ± 1.57 | 12.5 ± 1.74 | 12.8 ± 1.37 | .068 |
| APTT | 35.5 ± 3.57 | 35.8 ± 3.79 | 35.1 ± 3.32 | .295 |
| PT | 13.2 ± 0.97 | 13.4 ± 0.97 | 13.1 ± 0.95 | .007 |
| PT-INR | 1.0 ± 0.10 | 1.03 ± 0.10 | 1.00 ± 0.10 | .009 |
| CrCl (mL/min) | 73.7 ± 28.2 [n = 161#] | 62.9 ± 21.5 [n = 77#] | 83.6 ± 29.8 [n = 84#] | <.001 |
| Intraoperative hemorrhage volume (mL/kg) | 3.7 ± 2.75 [n = 147#] | 4.0 ± 3.17 [n = 70#] | 3.5 ± 2.26 [n = 77#] | .613 |
| Combined antithrombogenic drug use (±/unknown) | 31/136/0 | 19/61/0 | 12/75/0 | .114 |
| Combined P-glycoprotein inhibitor use (±/unknown) | 6/161/0 | 5/75/0 | 1/86/0 | .077 |

Data are expressed as the mean ± standard deviation or absolute values.

APTT = activated partial thromboplastin time, BMI = body mass index, CrCl = creatinine clearance, Hgb = hemoglobin, PT = prothrombin time, PT-INR = prothrombin time-international normalized ratio, THA = total hip arthroplasty, TKA = total knee arthroplasty.

**P* values were determined using the Mann–Whitney's *U* test or Fisher's exact test, as appropriate.

#Patients were excluded if data were lacking.

***3.2.4. A lower CrCl is a risk factor for anemia in patients undergoing Edx treatment, as revealed by multivariable logistic regression analysis.*** To identify the most important preoperative risk factors for anemia in patients undergoing Edx treatment after TKA/THA, multivariable logistic regression analysis was performed (Table 3B). Only CrCl was significantly correlated with a greater risk of Edx-associated anemia (OR: 1.034; 95% CI: 1.009–1.061; $P < .001$). The remaining variables (male sex, age, BW, and BMI) were not significantly associated with the incidence of anemia in patients undergoing Edx treatment.

***3.2.5. A lower preoperative CrCl is significantly associated with prolonged coagulation parameters during Edx treatment.*** The relationships between coagulation parameters during Edx treatment and preoperative CrCl were assessed (Fig. 2a–c). Preoperative CrCl was significantly correlated with coagulation parameters such as PT ($r = -0.352$; $P < .001$), PT-INR ($r = -0.356$; $P < .001$), and APTT ($r = -0.176$; $P = .030$). The correlations between preoperative CrCl and PT or PT-INR were stronger than those between preoperative CrCl and APTT.

***3.2.6. Relationships between preoperative CrCl and the degree and frequency of anemia and the usefulness of preoperative CrCl as a predictor of Edx-associated anemia.*** To evaluate the importance of preoperative CrCl in the development of anemia, the association between preoperative CrCl and the degree or frequency of anemia after surgery was investigated (Fig. 3a and b). A reduced preoperative CrCl was significantly correlated with reduced Hgb levels ($R = 0.278$; $P < .001$) (Fig. 3a). Additionally, a reduced preoperative CrCl was associated with an increased frequency of anemia (Fig. 3b). ROC curve analysis was performed to confirm the optimal cutoff value for CrCl as a preoperative predictor of Edx-associated anemia after surgery (Fig. 3c), revealing a value of 67.9 mL/min (area under the ROC curve: 0.722; sensitivity: 0.74; specificity: 0.68; $P < .001$). Thus, the preoperative CrCl is a critical risk factor for Edx-associated anemia.

**Table 3A**

**Univariable logistic regression analyses of risk factors for edoxaban-associated anemia.**

| Factors | OR | 95% CI | *P* value |
|---|---|---|---|
| Male sex | 2.303 | 1.041–5.329 | .044 |
| Age | 1.063 | 1.024–1.106 | .002 |
| Body weight | 0.965 | 0.938–0.992 | .012 |
| BMI | 0.862 | 0.790–0.934 | <.001 |
| CrCl | 0.969 | 0.954–0.982 | <.001 |
| PT | 1.391 | 0.985–2.121 | .089 |
| PT-INR | 24.85 | 0.881–1453 | .087 |

*P* values were determined using Fisher's exact test, as appropriate.
BMI = body mass index, CI = confidence interval, CrCl = creatinine clearance, OR = odds ratio, PT = prothrombin time, PT-INR = prothrombin time-international normalized ratio.

**Table 3B**

**Multivariable logistic regression analysis to identify significant risk factors for edoxaban-associated anemia.**

| Factors | OR | 95% CI | *P* value |
|---|---|---|---|
| Male sex | 0.445 | 0.116–1.577 | .220 |
| Age | 0.988 | 0.927–1.054 | .718 |
| Body weight | 0.949 | 0.868–1.034 | .237 |
| BMI | 1.199 | 0.964–1.505 | .108 |
| CrCl | 1.034 | 1.009–1.061 | <.001 |

*P* values were determined using Fisher's exact test, as appropriate.
BMI = body mass index, CI = confidence interval, CrCl = creatinine clearance, OR = odds ratio.

***3.2.7. Association of the CrCl cutoff value, as the detected risk factor for anemia, with Hgb levels, coagulation parameters, and RBC transfusion during Edx treatment.*** To clarify the effect of CrCl as a critical preoperative risk factor, the enrolled patients were divided into 2 groups based on the CrCl cutoff value (Fig. 3c): NRF (CrCl: ≥ 67.9 mL/min) group and LRF (CrCl: < 67.9 mL/min) group. The effect of this CrCl cutoff value on the Hgb levels, coagulation parameters, and RBC transfusion was compared between the LRF and NRF groups (Table 4 and Fig. 4). The number of patients who exhibited a reduction in the Hgb level of at least 2 g/dL was significantly greater in the LRF group than in the NRF group (39.3% vs 20.5%; $P = .011$) (Table 4).

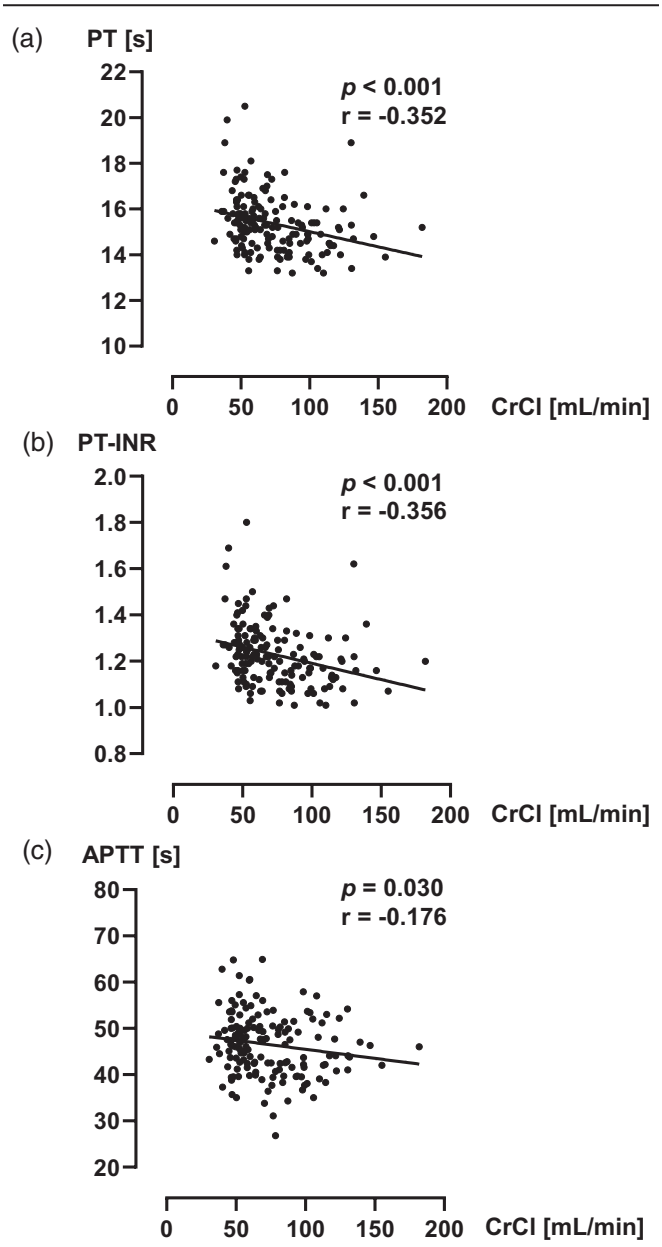


**Figure 2.** Correlation between preoperative CrCl and coagulation parameters. Preoperative CrCl significantly correlated with both PT and PT-INR (a, b). These correlations were stronger than the correlation between preoperative CrCl and APTT (c). Correlations were evaluated using Spearman's correlation coefficient. The *P* values and *r* values (correlation coefficients) are shown in each figure. APTT = activated partial thromboplastin time, CrCl = creatinine clearance, PT = prothrombin time, PT-INR = prothrombin time-international normalized ratio.

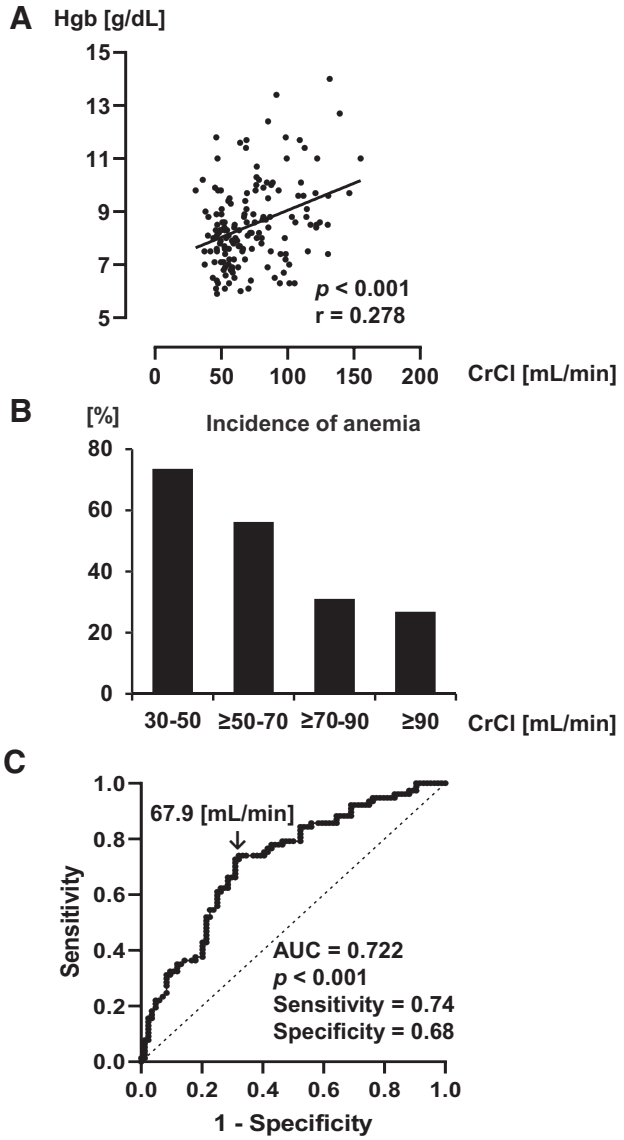


**Figure 3.** Effects of preoperative CrCl on the degree and frequency of edoxaban-associated anemia and the usefulness of preoperative CrCl as a predictor of edoxaban-associated anemia. Preoperative CrCl significantly correlated with Hgb levels on POD 3 (a). The incidence of edoxaban-associated anemia increases as preoperative CrCl decreases (b). The optimal preoperative CrCl cutoff value for predicting edoxaban-associated anemia was calculated using the AUC and was 67.9 mL/min. The AUC, *P* value, sensitivity, and specificity values obtained at the optimal cutoff values are shown. Correlations were evaluated using Spearman's correlation coefficient. AUC = area under the ROC curve, CrCl = creatinine clearance, Hgb = hemoglobin, POD = postoperative day.

The frequency of received blood transfusions in the LRF group was also higher than that in the NRF group (40.5% vs 15.7%; $P < .001$). Overall, the LRF group demonstrated a significantly higher frequency of Edx-associated anemia than the NRF group (67.9% vs 27.7%; $P < .001$). Regarding coagulation parameters, PT and PT-INR during Edx treatment were significantly higher in the LRF group than in the NRF group, except on POD 10, although no significant differences were found between the groups during the preoperative day (Fig. 4a and b). However, the APTT did not differ significantly between the groups (Fig. 4c). The Hgb levels were also significantly lower in the LRF group than in the NRF group, except on POD 10 (Fig. 4d).

**Table 4**

**Frequency of edoxaban-associated anemia after orthopedic surgery based on renal function.**

| Events | CrCl < 67.9 mL/min [n = 84] | CrCl ≥ 67.9 mL/min [n = 83] | *P*-value |
|---|---|---|---|
| Reduction in Hgb level of at least 2 g/dL (±) | 33/51 | 17/66 | .011 |
| Administration of blood transfusion (±) | 34/50 | 13/70 | <.001 |
| Anemia (±) | 57/27 | 23/60 | <.001 |

Data are expressed as absolute values. *P* values were determined using Fisher's exact test.
CrCl = creatinine clearance, Hgb = hemoglobin.

## 4. Discussion

The main finding of the present study was that Edx treatment was associated with an increased risk of anemia-related events, as determined through pharmacovigilance analyses of large-scale spontaneous reporting systems databases. Furthermore, in the present study, a reduction in renal function was a critical risk factor for Edx-associated anemia, accompanied by increased coagulation parameter values.

Pharmacovigilance analyses using the FAERS and JADER databases revealed a clear association between Edx treatment and increased anemia-related events. In patients with lower limb orthopedic disease, Edx treatment was significantly associated with an increase in anemia-related events relative to patients receiving fondaparinux and warfarin. These results are similar to those of previous studies.[5,6] This finding suggests that patients treated with Edx should be closely monitored for anemia. Responses to Edx also exhibit interindividual and individual variability based on patient characteristics, which may affect patient safety.[18]

In the present study, a lower preoperative CrCl was associated with an increased frequency of Edx-associated anemia. Additionally, a significant correlation was found between preoperative CrCl and PT & PT-INR during Edx treatment. These findings are comparable to previous reports of an association between Edx treatment and coagulation parameters.[5,6,18–20] The prolongation of these coagulation parameters after Edx administration depends on the plasma Edx concentration.[18–20] Therefore, patients with decreased preoperative CrCl were at an increased risk of anemia accompanied by an increase in their blood Edx concentration.

Additionally, preoperative CrCl was significantly correlated with the degree of anemia noted during Edx treatment, as assessed based on Hgb levels. ROC curve analysis also showed that a preoperative CrCl cutoff value of 67.9 mL/min was significantly associated with anemia during Edx treatment, with good sensitivity. Thus, reduced renal function is a critical risk factor for Edx-associated anemia. Assessing patients' renal function before starting Edx treatment may be crucial for managing Edx-associated anemia.

Interestingly, patients with preoperative CrCl values < 67.9 mL/min had significantly lower preoperative Hgb levels and a greater frequency of anemia than those with CrCl values ≥ 67.9 mL/min. A lower baseline Hgb level was also a significant risk factor for bleeding in Japanese patients receiving Edx.[21] The implications of this association between the baseline Hgb levels and renal function for Edx treatment are interesting and should be investigated further.

### *4.1. Limitations*

The present study had several limitations. First, some data were missing from the FAERS and JADER databases; therefore, some adverse event reports were not included in this

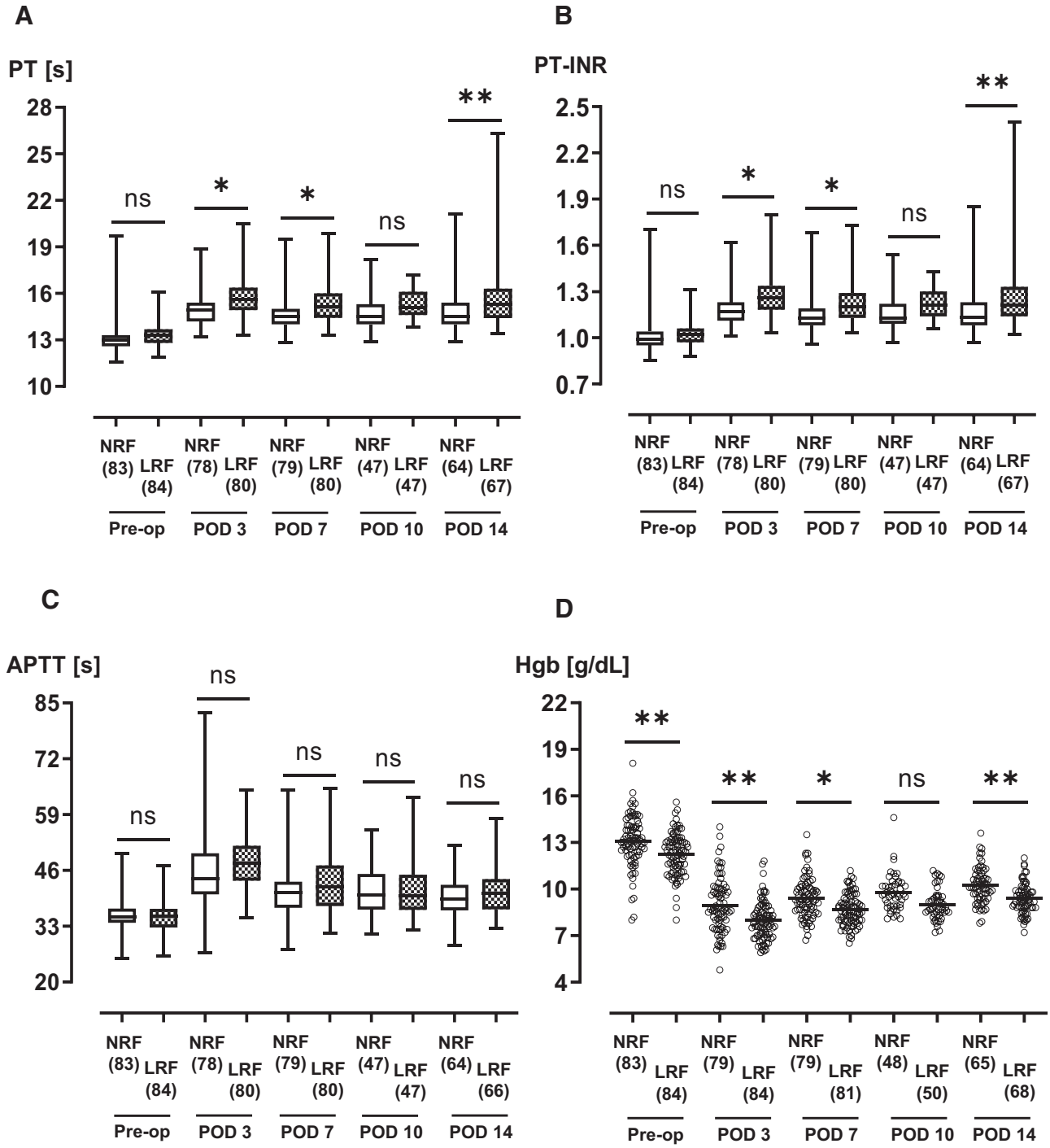


**Figure 4.** Serial changes in the PT (a), PT-INR (b), APTT (c), and Hgb (d) values during edoxaban treatment in patients with or without decreased renal function. The 3 coagulation parameters were prolonged during edoxaban treatment. Both PT and PT-INR were significantly longer in the NRF group than in the LRF group from POD 3 to 14, except on POD 10. However, APTT did not differ significantly between the groups at any time point. The Hgb levels decreased, particularly on POD 3 during edoxaban treatment, and the LRF group exhibited significantly lower Hgb levels than the NRF group from the preoperative day to POD 14, except on POD 10. The significance of the differences was determined using ANOVA, followed by Tukey's multiple comparison test. *$P < .05$ and **$P < .01$ between the groups at each timepoint; ns: no significant difference, NRF: patients with normal renal function (CrCl: ≥ 67.9 mL/min), LRF: patients with lower renal function (CrCl: < 67.9 mL/min), ANOVA = analysis of variance, APTT = activated partial thromboplastin time, CrCl = creatinine clearance, Hgb = hemoglobin, LRF = low renal function, NRF = normal renal function, POD = postoperative day, PT = prothrombin time, PT-INR = prothrombin time-international normalized ratio, Preop = preoperative day.

pharmacovigilance study. Second, the present retrospective study was a secondary analysis of a previous study performed at a single center.[5,6] Therefore, the study design did not allow for randomization; missing data were also excluded from the analysis, and the sample size was not controlled. The retrospective nature of this study might have introduced bias into the results. Third, the Cockroft-Gault Index is an indirect index of renal function because this index is influenced by body weight, age, and sex. However, we used this index because it is used as one of several standard dose adjustment

factors of Edx.[2,3] Fourth, the renal function (CrCl) cutoff value was solely determined using this retrospective study population. Multicenter prospective studies are required to validate our findings.

## 5. Conclusion

Edx treatment was associated with an increased number of anemia-related events in orthopedic patients. Decreased renal function was a risk factor for Edx-associated anemia after orthopedic surgery.

## Author contributions

**Conceptualization:** Yasuhisa Izushi, Yoichiro Takami, Soichiro Ushio, Naofumi Shiota.
**Data curation:** Yasuhisa Izushi, Hiroshi Yamamoto.
**Formal analysis:** Yasuhisa Izushi, Yoichiro Takami, Soichiro Ushio, Tomonori Tetsunaga, Naofumi Shiota.
**Investigation:** Yasuhisa Izushi, Yoichiro Takami, Naofumi Shiota.
**Methodology:** Yasuhisa Izushi, Yoichiro Takami, Naofumi Shiota, Toru Sato.
**Project administration:** Yasuhisa Izushi, Naofumi Shiota, Toru Sato.
**Resources:** Yasuhisa Izushi, Tomonori Tetsunaga, Naofumi Shiota, Toru Sato.
**Supervision:** Yasuhisa Izushi, Naofumi Shiota, Hiroshi Yamamoto, Yoshihisa Kitamura.
**Validation:** Yasuhisa Izushi, Yoichiro Takami, Soichiro Ushio.
**Visualization:** Yasuhisa Izushi, Tomonori Tetsunaga, Naofumi Shiota.
**Writing – original draft:** Yasuhisa Izushi, Yoichiro Takami.
**Writing – review & editing:** Yasuhisa Izushi, Yoichiro Takami, Soichiro Ushio, Tomonori Tetsunaga, Naofumi Shiota, Yoshihisa Kitamura.

## References


[1] Eikelboom JW, Quinlan DJ, Hirsh J, et al. Laboratory monitoring of non-vitamin K antagonist oral anticoagulant use in patients with atrial fibrillation: a review. JAMA Cardiol. 2017;2:566–74.
[2] US Food and Drug Administration. FDA Drug Databases web site of SAVAYA®tablets (edoxaban). Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=206316 [access date September 29, 2021].
[3] The European Medicines Agency. Medicines web site of ROTEAS®tablets (edoxaban). Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/roteas [access date September 29, 2021].
[4] Daiichi Sankyo Limited. Daiichi Sankyo launches LIXIANA®tablets (edoxaban), a direct oral factor Xa inhibitor, in Japan for the prevention of venous thromboembolism after major orthopedic surgery: first direct oral factor Xa inhibitor available to Japanese patients. Available at: https://www.daiichisankyo.co.jp/media/press_release/detail/index_6185.html [access date September 29, 2021].
[5] Izushi Y, Takami Y, Shiota N, et al. Clinical assessment of postoperative anemia associated with edoxaban in patients undergoing total knee arthroplasty compared to fondaparinux. Biol Pharm Bull. 2016;39:516–23.
[6] Izushi Y, Shiota N, Tetsunaga T, et al. The clinical impact of edoxaban for the patients with postoperative anemia after total hip arthroplasty. Eur J Orthop Surg Traumatol. 2018;28:1349–58.
[7] Steuber TD, Howard ML, Nisly SA. Strateries for the management of postoperative anemia in elective orthopedic surgery. Ann Pharmacother. 2016;50:578–85.
[8] Spahn DR. Anemia and patient blood management in hip and knee surgery: a systematic review of the literature. Anesthesiology. 2010;113:482–95.
[9] Enokiya T, Hasegawa M, Morikawa Y, et al. Postoperative anaemia is a risk factor for bleeding-related event in thromboprophylaxis using fondaparinux sodium injection after total knee or hip arthroplasty. Biol Pharm Bull. 2020;43:266–71.
[10] US Food and Drug Administration. FDA Adverse Event Reporting System web site. Available at: https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-latest-quarterly-data-files [access date April 3, 2021].
[11] Pharmaceuticals and Medical Devices Agency. Japanese Adverse Drug Event Report database web site. Available at: https://www.pmda.go.jp/safety/info-services/drugs/adr-info/suspected-adr/0003.html [access date February 16, 2021].
[12] Hagiwara H, Fukuta H, Niimura T, et al. Comparison of hemorrhagic risk between prasugrel and clopidogrel: a retrospective study using adverse drug event reporting databases. Int J Med Sci. 2020;17:728–33.
[13] Sasaki H, Ishida K, Shibanuma N, et al. Retrospective comparison of three thromboprophylaxis agents, edoxaban, fondaparinux, and enoxaparin, for preventing venous thromboembolism in total knee arthroplasty. Int Orthop. 2014;38:525–9.
[14] Schulman S, Angerås U, Bergqvist D, et al. Subcommittee on control of anticoagulation of the scientific and standardization committee of the international society on thrombosis and haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost. 2010;8:202–4.
[15] Suzuki Y, Suzuki H, Umetsu R, et al. Analysis of the interaction between clopidogrel, aspirin, and proton pump inhibitors using the FDA adverse event reporting system database. Biol Pharm Bull. 2015;38:680–6.
[16] Hair JF Jr, Anderson RE, Tatham RL, et al. Multivariate data analysis. 3rd ed. New York: Macmillan; 1995.
[17] Joo J, Moon HK, Moon YE. Identification of predictors for acute postoperative pain after gynecological laparoscopy (STROBE-compliant article). Medicine (Baltim). 2019;42:e17621.
[18] Testa S, Dellanoce C, Paoletti O, et al. Edoxaban plasma levels in patients with non-valvular atrial fibrillation: inter and intra-individual variability, correlation with coagulation screening test and renal function. Thromb Res. 2019;175:61–7.
[19] Ogata K, Mendell-Harary J, Tachibana M, et al. Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. J Clin Pharmacol. 2010;50:743–53.
[20] Wolzt M, Samama MM, Kapiotis S, et al. Effect of edoxaban on markers of coagulation in venous and shed blood compared with fondaparinux. Thromb Haemost. 2011;105:1080–90.
[21] Takase T, Ikesue H, Nakagawa H, et al. Risk factors for major bleeding and clinically relevant non-major bleeding in Japanese patients treated with edoxaban. Biol Pharm Bull. 2020;43:458–62.