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Analysis of a large dataset to identify predictors of blood transfusion in primary total hip and knee arthroplasty

ZeYu Huang^{1,†}, Cheng Huang^{2,†}, JinWei Xie^{1,†}, Jun Ma^{1,†}, GuoRui Cao¹, Qiang Huang¹, Bin Shen^{1,**}, Virginia Byers Kraus^{3,4}, and FuXing Pei^{1,*}

¹Department of Orthopedic Surgery, West China Hospital, West China Medical School, SiChuan University, ChengDu, SiChuan Province, People's Republic of China

²College of Cybersecurity, ChengDu, SiChuan Province, People's Republic of China

³Duke Molecular Physiology Institute, Duke University School of Medicine, Duke University, Durham, NC, United States

⁴Division of Rheumatology, Department of Medicine, Duke University School of Medicine, Duke University, Duke University, Durham, NC, United States

Abstract

Background—The aim of this study was to identify the predictors of need for allogenic blood transfusion (ALBT) in primary lower limb total joint arthroplasty (TJA).

Study design and Methods—This study utilized a large dataset of 15,187 patients undergoing primary unilateral TJA. Risk factors and demographic information were extracted from the electronic health record. A predictive model was developed by both a random forest (RF) algorithm and logistic regression (LR). The area under the receiver operating characteristic curve (AUC-ROC) was used to compare the accuracy of the two methods.

Results—The rate of ALBT was 18.9% in total. Patient-related factors associated with higher risk of an ALBT included female sex (OR=1.26, $p<0.001$), American Society of Anesthesiologists (ASA) II (OR=1.32, $p<0.001$), ASAIII (OR=1.65, $p<0.001$) and ASAIV (OR=2.92, $p<0.001$). Surgery-related risk factors for ALBT were operative time (OR=1.00, $p<0.001$), drain use (OR=2.48, $p<0.001$) and amount of intraoperative blood loss (OR=1.003, $p<0.001$). Higher preoperative Hb (OR=0.99, $p<0.001$) and tranexamic acid (TXA) use (OR=0.43, $p<0.001$) were associated with decreased risk for ALBT. The RF model had a better predictive accuracy (AUC 0.84) than the LR model (AUC 0.77) ($p<0.001$).

Conclusion—The risk factors identified in the current study can provide specific, personalized perioperative ALBT risk assessment for a patient considering lower limb TJA. Furthermore, the

*Corresponding Author: FuXing Pei, Professor of Medicine, Department of Orthopedic Surgery, West China Hospital, West China Medical School, Sichuan University, 37# Wainan Guoxue Road, Chengdu, Sichuan Province, People's Republic of China, Tel: +86-18980601380/ Fax: +86-028-85423848, peifuxing1951@163.com. **Co-Corresponding author: Bin Shen, Professor of Medicine, Department of Orthopedic Surgery, West China Hospital, West China Medical School, Sichuan University, 37# Wainan Guoxue Road, Chengdu, Sichuan Province, People's Republic of China, Tel: +86-18980601390/ Fax: +86-028-85423848, 492385233@qq.com.
†ZeYu Huang, Cheng Huang, JingWei Xie and Jun Ma contributed equally to this work.

Conflict of Interest:

The authors declare that they have no conflict of interest.

predictive accuracy of the RF algorithm was significantly higher than that of LR, making it a potential tool for future personalized preoperative prediction of risk for perioperative ALBT.

Keywords

total joint arthroplasty; total hip arthroplasty; total hip arthroplasty; transfusion; risk factors; random forest analysis

Introduction

Each year, over 13 million units of allogeneic packed red blood cells are transfused in the United States¹, with patients undergoing surgery comprising the majority of recipients². The 2004 Nationwide Inpatient Sample database analysis by Morton et al.³ demonstrated that hip and knee arthroplasty were among the top 10 most frequent procedures requiring blood product transfusion. The community of orthopaedic surgeons have made great efforts to minimize the utilization of blood transfusions in patients undergoing total hip and knee arthroplasty (THA and TKA) based on studies demonstrating associations of blood transfusion with serious complications such as perioperative infection^{4,5}, prolonged hospital stay⁵, deep vein thromboembolism^{6,7} and increased in-hospital mortality^{5,8,9}.

The ability to preoperatively predict the perioperative need for blood transfusion has been a challenge for joint surgeons for a long time. Several prior studies have reported the predictors associated with the need for blood transfusion in THA and TKA. Despite identification of a number of predictors including blood volume, weight, age, estimated blood loss, drug use, female sex, preoperative hemoglobin (Hb) level and comorbidities, overall generalizability to different practices or cases, is still in question¹⁰. Lack of a validated model to predict likelihood of transfusion serves as an impediment to benchmarking and guiding quality improvement. Further, such a model could help guide individualized care and therapeutic strategies to reduce transfusion in patients at risk.

Machine-learning algorithms can be used to predict the outcome of a new observation; these algorithms are based on a training data set containing previous observations where the outcome is known. Among these algorithms, random forest (RF) analysis is most commonly used in medical care. It has been used in cheminformatics to predict chemical compound activities¹¹, for selecting single-nucleotide polymorphisms predictive of phenotypes¹², for predicting survival outcomes¹³ and for identifying the risk factors for complications of cataract surgery¹⁴. However, RF has not yet been applied to the challenge of predicting the need for blood transfusion in total joint arthroplasty (TJA).

From 2013 to 2016, a multicenter study on the efficacy and safety of perioperative management of THA and TKA was conducted in China. A large database containing 15,187 patients has been established. This database was used to fulfill the following aims: (1) Identify the predictors of blood transfusion in primary THA and TKA using logistic regression and RF; (2) Compare the predictive capacity of RF with a logistic regression model.

Materials and Methods

Data Source

This study was a secondary analysis of a large dataset generated from a prospective multicenter study on the efficacy and safety of perioperative management of THA and TKA. Transfusion criteria included symptomatic anemia (light-headedness, presyncope, fatigue precluding participation in the therapy, palpitation, or shortness of breath not due to other causes) with Hb between 70-100 g/L or any Hb below 70 g/L. The majority of allogenic blood transfusion (ALBT) occurred after surgery (98.9%), while only 1.1% occurred during surgery and no ALBT occurred preoperatively. This database constitutes patient-level hospital-discharge data provided by 26 university teaching hospitals in China (10 national and 16 regional hospitals) sponsored by the Chinese Health Ministry (201302007) (Supplemental Table 1). Data elements included patient demographic variables, diagnosis, procedure codes, hospital characteristics and in-hospital mortality. We confirmed the completeness and validity of the data by comparison with data from hospital information systems (HISs); we specifically checked for missing data or incorrectly coded values in the current database. This study was deemed exempt by the hospital's Institutional Review Board (2012-268).

Study Population

We identified cases of primary THA and TKA by the presence of the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) procedure codes. We excluded discharge records carrying ICD-10-CM diagnosis codes for acute arthroplasty, a complication of previous arthroplasty, a bilateral lower-extremity arthroplasty, metastatic and/or bone cancer, lower-extremity fractures, or a joint dislocation. American Society of Anesthesiologists (ASA) class was determined by an anesthetist before the surgery and recorded¹⁵. We also excluded patients younger than age eighteen. The total number of patients included in the study was 15,187. Patients who received an autologous blood transfusion rather than an allogenic blood product were excluded from all analyses.

Statistical analyses

Independent t-tests were used for continuous variables and Chi-squared test or Fisher exact test to assess the differences of proportions between the transfusion and non-transfusion groups. In order to predict the need for ALBT, we first researched the previous literature and included thirteen ALBT related factors as follows: age, gender, body mass index (BMI), ASA classification, preoperative Hb, preoperative analgesic use, type 2 diabetes, hypertension, tranexamic acid (TXA) use, drain use and intraoperative blood loss. We then utilized the RF algorithm and logistic regression to build an automatic classification model¹⁶ to determine the independent predictors of transfusion. For predictors of binary variables such as gender, type 2 diabetes and hypertension, we used 0 and 1 to represent the value. For the other predictors, feature normalization was performed to fit them into a value between 0 and 1. To compare the predictive ability of logistic regression and random forest models, the performance of each model was evaluated based on the area under the curve (AUC) of the receiver-operating characteristic (ROC) using a fivefold cross-validation method. Validation entailed training the model with four subsets, testing with the remaining subset and

recalculating the resulting AUC, then repeating this procedure five times and averaging the results. The relative performance of the two models was examined by overall predictive value (NPV) and positive predictive value (PPV). In the logistic regression models, a cutoff outcome probability of 50% was used for classification. A p value of <0.05 was considered significant. Since 12 clinical parameters were assessed, the statistical significance for multiple regression was further evaluated using the conservative Bonferroni p value ($0.05/12=0.004$). All statistical analyses were conducted in Python Version 2.7 (Python Software Foundation, Wilmington, Delaware, USA).

Results

Data completeness Analysis

Based on comparison with data from the HIS, completeness of reporting was 92% for primary THA and 94% for TKA. The portion of missing or incorrectly coded values of variables was generally less than 0.5%.

Patient population and demographics

Demographic characteristics of the population are shown in Table 1. Our population was predominantly female (66.0% vs. 34.0% male). The mean age at the time of surgery was 62.0 years (standard deviation [SD] 14.9). The overall allogenic blood transfusion (ALBT) rate in patients undergoing primary THA and TKA in the large dataset was 18.9% (22.1% for THA, 15.8% for TKA). Totally, the ALBT and non-ALBT groups were significantly different in terms of age, BMI, ASA class, preoperative Hb, preoperative hematocrit (Hct), preoperative analgesic use, type 2 diabetes, operative time, TXA use, drain use and intraoperative blood loss (Table 1). The ALBT and non-ALBT groups in primary THA were significantly different in terms of ASA class, preoperative Hb, preoperative Hct, preoperative analgesic use, hypertension, operative time, TXA use, drain use and intraoperative blood loss (Supplemental Table 2). The ALBT and non-ALBT groups in primary TKA were statistically different in age composition, BMI, ASA class, preoperative Hb, preoperative analgesic use, tourniquet use, type 2 diabetes, hypertension, operative time, TXA use, drain use and intraoperative blood loss (Supplemental Table 3).

Risk factors for ALBT in multivariable logistic regression analysis

The multivariable logistic regression analysis revealed a number of independent risk factors for perioperative ALBT in patients of the total dataset (Table 2). Patient-related factors associated with significantly increased risk for ALBT were female sex, ASAIL, ASAILI and ASAILV. Surgery-related factors associated with significantly increased risk for ALBT were operative time, drain use and intraoperative blood loss. Higher preoperative Hb and TXA use was associated with decreased risk of perioperative ALBT (Table 2).

In primary THA, risk factors independently associated with ALBT in the multivariable analysis included ASAIL, ASAILI, ASAILV, drain use and intraoperative blood loss (Supplemental Table 4). Higher perioperative Hb and TXA use were associated with decreased risk of perioperative ALBT (Supplemental Table 4).

In primary TKA, risk factors independently associated with ALBT in the multivariable analysis included preoperative nonsteroidal anti-inflammatory drug (NSAID) use, full-time use of a tourniquet (defined as a tourniquet inflated before the incision and deflated after the closure of the incision), part-time use of a tourniquet (defined as a tourniquet inflated before the incision and deflated after the hardening of the cement), operative time, drain use and intraoperative blood loss (Supplemental Table 5). Higher preoperative Hb and TXA use were associated with decreased risk of perioperative ALBT (Supplemental Table 5).

RF analysis and predictive modeling comparison

RF analysis of the total dataset identified ten top-ranked predictive variables: age, sex, BMI, hypertension, type 2 diabetes, ASA class, TXA use, intraoperative blood loss, drain use and preoperative Hb. While RF analysis was applied to datasets of primary THA and TKA separately, the ten top-ranked predictive variables were the same as those identified in the total data.

Validation in the total dataset suggested that the RF model had a modest but statistically significantly better accuracy (AUC 0.84 [95% confidence interval [CI] 0.81-0.87]) than the logistic regression model (AUC 0.77 [95% CI 0.74-0.79]) ($p < 0.001$) (Figure 1). The results of the predictive modeling in THA and TKA datasets were consistent, revealing better predictive accuracies in a RF model than a logistic regression model (AUC 0.83 [95% CI 0.79-0.86] vs. 0.78 [95% CI 0.73-0.83], $p < 0.001$; AUC 0.85 [95% CI 0.80-0.89] vs. 0.78 [95% CI 0.73-0.84], $p < 0.001$; respectively) (Figures 2 and 3). The overall NPV and PPV for the LR model were 18.0% and 80.6% respectively. The overall NPV and PPV for the RF model were 16.2% and 80.4% respectively.

Discussion

Though the occurrence of substantial blood loss has dramatically decreased over the last two decades¹⁷, blood loss continues to be a present and future concern in TJA. The aging arthroplasty population is less tolerant of prolonged postoperative anemia and is therefore more likely to require perioperative transfusion. Previous studies have addressed the risks associated with transfusion to develop a standardized transfusion strategy and determine whether it is necessary for additional monitoring of transfused patients^{18,19}. The advent of data mining, machine learning and artificial intelligence provide the means of constructing a personalized system for preoperative prediction of the need for a perioperative transfusion in TJA. Using our established large dataset we identified the following as the most important findings of the present study: (1) based on logistic regression, 4 patient-related factors and 3 surgery-related factors highly associated with increased ALBT in TJA; 1 patient-related and 1 surgery-related factors were associated with decreased risk of ALBT in TJA; (2) based on an RF algorithm, the top 10 ranking features for ALBT were highly consistent in TJA, THA and TKA data; (3) the RF algorithm had a better accuracy than logistic regression in predicting transfusion in TJA, THA and TKA.

As previously reported based on other large databases^{5,18-20}, the ALBT rate of primary THA and TKA ranged from 15.0% to 22.2%. Our result was comparable with these reports with a total ALBT rate of 18.9% (22.1% for THA, 15.8% for TKA). The logistic regression

analysis in the current study provides important insight into patients and surgery-related factors that influence the risk of transfusion. In agreement with previous reports²¹⁻²³, increased risk of ALBT was predicted by female gender, a higher ASA class, lower preoperative Hb, longer operative time and more intraoperative blood loss after TJA^{5,18-20}. Although several studies reported a correlation between increased perioperative blood loss and decreased risk of blood transfusion requirements in THA and TKA^{5,18,19}, some other studies have reported no statistically significant relationship between BMI, blood loss and transfusion risk²⁴⁻²⁷. A number of studies reporting a positive correlation between BMI and transfusion risk did not stratify patient groups using the BMI classification system set forth by the WHO^{27,28}. In our current study, higher BMI was associated with decreased risk of ALBT in TKA but not THA. The generalizability of this finding needs to be evaluated in western populations. The Chinese have a relatively narrow distribution of BMI, which means data may be insufficient with respect to extreme BMI values (such as BMI>30kg/m²). Thus, we still need to accumulate these data to optimize the predictive model. Few prior studies have used large dataset to evaluate the association of preoperative analgesic use and ALBT risk in TJA. According to the information provided by our database, ALBT risk in THA would not increase based on perioperative analgesic or NSAID drug use. Rather NSAID drug use is only an independent risk factor for ALBT in TKA.

With regard to the surgery-related factors, we identified that tourniquet use (both full-time and part-time use) is a strong risk factor for ALBT in TKA. This is consistent with the findings of a large number of previous studies²⁹⁻³¹ showing that tourniquet use could reduce intraoperative blood loss but would cause greater postoperative blood loss and hidden blood loss. As reported by several meta-analyses, drain use was also found to be a risk factor for ALBT³²⁻³⁵. We believed it might be a consequence of absence of blood loss into the drain. TXA use is a much debated topic in the field of joint replacement^{21-23,35}. In agreement with previous studies, we found TXA use to be associated with a reduced risk of ALBT^{21-23,35}. Owing to these findings, currently drains and tourniquets are not routinely used in our orthopaedic center's daily practice. TXA is applied to all possible surgical candidates without contraindications to its use such as any history of blood clot events within 6 months.

As the performance of fast-track surgery has increased, a greater focus has been placed on the study of the influence of patients' comorbidities on the outcomes of joint arthroplasty. For instance, in the United States, Bolognesi et al.³⁶ identified diabetes to be a strong factor of transfusion in both primary THA (odds ratio [OR] 1.3, 95% CI [1.2-1.3]) and TKA (OR 1.2, 95% CI [1.1-1.3]). In another study of 1,030,013 subjects, Marchant et al.³⁷ illustrated that both controlled and uncontrolled diabetes were strong risk factors for perioperative transfusion. In our current study, we identified type 2 diabetes as a risk factor for perioperative ALBT in the total dataset (OR 1.26, 95% CI [1.04-1.52]) and TKA (OR 1.32, 95% CI [1.02-1.69]) but not THA. However, after Bonferroni correction, neither of them reached statistical significance. The number of type 2 diabetes patients included in our database was relatively small in comparison with the two previous studies making it less likely to be detected as a risk factor for ALBT in our study.

The literature suggests that hypertension has divergent effects on ALBT. Several big data studies show that hypertension is a risk factor for ALBT in association with lower limb

arthroplasty^{5,38,39}; other studies failed to identify hypertension as a risk factor⁴⁰⁻⁴². Our multivariable analysis in the current study did not suggest hypertension as a risk factor for ALBT. In a previous study, Pola et al.⁴² observed that patients with hypertension who underwent THA had significantly higher total blood loss (1707 vs. 1474 mL, respectively; $p=0.02$). However, these patients did not have a significant increased risk of transfusion. In addition, they noted that when hypertension was combined with female sex, age greater than 75 years, or a BMI less than 27 kg/m², the rate of transfusion was statistically significantly elevated. These data suggest that hypertension might synergize with other independent risk factors of ALBT.

RF is a tree-based, non-parametric data mining/machine learning method requiring no assumption about data distribution¹⁶. In recent years, various research groups have applied RF to investigate various healthcare-related questions including prediction of: hospital readmissions⁴³; adverse drug reactions⁴⁴; incident diabetes⁴⁵; and congenital heart defects⁴⁶. The RF algorithm turned out to be a better choice in many scenarios compared with other machine learning algorithms, since it combines the six properties that are all important in healthcare scenarios⁴⁷: (1) it does not overfit; (2) it is robust to noise; (3) it has an internal mechanism to estimate error rate; (4) it provides indices of variable importance; (5) it naturally works with mixes of continuous and categorical variables; (6) it can be used for data imputation and cluster analysis. To our knowledge, the current study is the first to apply an RF algorithm to predict need for blood transfusion in TJA and to compare its accuracy with logistic regression. In determining the variable importance, RF showed high consistency within the three subgroupings of the dataset (total, THA and TKA). Moreover, compared with logistic regression, the RF algorithm showed improved predictive accuracy (5%-7%) in all three subgroupings of the dataset.

There are several limitations to this study. First, this study only contained the records of several comorbidities other than all pre-existing conditions; this prevented us from further exploring the influence of other comorbidities on perioperative ALBT. Second, information on level of control of type 2 diabetes and hypertension was not recorded in detail in the database, thus we were unable to determine the extent to which these comorbidities influenced the need for perioperative ALBT. Third, the number of patients with extreme BMI (BMI>30kg/m²) and ASA class (ASA V) was relatively small in the current database. Fourth, the RF algorithm is a multitude of decision trees that can be difficult to interpret. Although RF are biased in favor of attributes with multiple levels, our dataset included categorical variables. Thus, alternative machine learning based prediction models warrant further study. Fifth, we did not use datasets from other populations and nationalities to validate our model. Thus, the power of the current proposed predictive model may be reduced for patients from other populations.

In conclusion, we identified 4 patient-related factors and 3 surgery-related preoperative factors that were strongly associated with an increased risk of ALBT in lower limb TJA. The best RF cross-validated algorithm was 84% accurate for predicting the need for perioperative ALBT. We are working to create an on-line predictive system (called Transfusion Risk Assessment Tool for TJA) to serve joint surgeons internationally. Future work is needed to verify and optimize the current predictive model in other datasets from different populations

to guide joint surgeons in choosing the most appropriate blood management strategy for each patient in order to minimize transfusions and optimize patient clinical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Receiver operating characteristic (ROC) curve comparison of logistic regression (LR) and random forest (RF) algorithm models of the dataset of total. AUC=area under the curve

Figure 2.

Receiver operating characteristic (ROC) curve comparison of logistic regression (LR) and random forest (RF) algorithm models of the dataset of total hip arthroplasty (THA).

AUC=area under the curve

Figure 3. Receiver operating characteristic (ROC) curve comparison of logistic regression (LR) and random forest (RF) algorithm models of the dataset of total knee arthroplasty (TKA). AUC=area under the curve

Table 1

Patient demographics and perioperative factors in dataset of total

Perioperative factors	Total (n=15187)	Transfusion (n=2867)	Non-transfusion (n=12320)	p value
Age				
Mean age (years) (SD)	62.0±14.9	61.3±13.3	62.2±15.2	<0.001
Age<65 (n, %)	8008 (100%)	1584 (19.8%)	6424 (80.2%)	
65 Age<75 (n, %)	5004 (100%)	857 (17.1%)	4147 (82.9%)	
75 Age<85 (n, %)	2011 (100%)	384 (19.1%)	1627 (80.9%)	
Age 85 (n, %)	164 (100%)	42 (25.6%)	122 (74.4%)	
Gender				
Gender (male) (n, %)	5159 (100%)	1005 (19.5%)	4154 (80.5%)	0.175
Gender (female) (n, %)	10028 (100%)	1862 (18.6%)	8166 (81.4%)	
Mean BMI (SD)	24.9±4.3	24.5±4.9	24.9±4.2	<0.001
ASA class				
ASAI(n, %)	5387 (100%)	923 (17.1%)	4464 (82.9%)	<0.001
ASAI(n, %)	8219 (100%)	1456 (17.7%)	6763 (82.3%)	
ASAI(n, %)	1516 (100%)	459 (30.3%)	1057 (69.7%)	
ASAI(n, %)	56 (100%)	26 (46.4%)	30 (53.6%)	
ASAI(n, %)	9 (100%)	3 (33.3%)	6 (66.7%)	
Mean preoperative Hb (SD)	129.5±16.6	128.0±17.3	130.0±16.5	<0.001
Mean preoperative Hct (SD)	39.2±5.2	38.7±6.2	39.3±4.9	<0.001
Preoperative analgesic use (n, %)	3774 (100%)	584 (15.5%)	3190 (84.5%)	<0.001
Type 2 diabetes (n, %)	804 (100%)	185 (23.0%)	619 (73.0%)	0.002
Hypertension (n, %)	3150 (100%)	627 (19.9%)	2523 (80.1%)	0.101
Operative time (min) (SD)	93.9±51.9	111.5±58.6	89.8±49.3	<0.001
TXA use (n, %)	8190 (100%)	956 (11.7%)	7234 (88.3%)	<0.001
Drain use (n, %)	10946 (100%)	2362 (21.6%)	8584 (78.4%)	<0.001
Intraoperative blood loss (mL)	223.5±268.6	409.6±448.5	180.2±179.4	<0.001

Abbreviations: SD, standard deviation; BMI, body mass index; ASA, American Society of Anesthesiologists; Hb, hemoglobin; Hct, hematocrit; min, minute; TXA, tranexamic acid. *p* value calculated using independent t-test, Pearson chi-square test or Fisher exact test.

Table 2

Multivariate logistic regression analysis of Transfusion in dataset of total

Perioperative factors	OR	95% CI	<i>p</i> value
BMI	0.99	0.98-1.00	0.177
Age			
Age<65	1.00 (Reference)	-	-
65 Age<75	0.99	0.89-1.10	0.890
75 Age<85	1.18	1.02-1.35	0.024
Age 85	1.36	0.93-1.99	0.111
Gender			
Gender (male)	1.00 (Reference)	-	-
Gender (female)	1.26	1.14-1.40	<0.001 [†]
ASA class			
ASA I	1.00 (Reference)	-	-
ASA II	1.32	1.19-1.46	<0.001 [†]
ASA III	1.65	1.42-1.92	<0.001 [†]
ASA IV	2.92	1.60-5.35	<0.001 [†]
ASA V	1.18	0.21-6.54	0.848
Mean preoperative Hb	0.99	0.99-0.99	<0.001 [†]
Preoperative analgesic use			
Preoperative non-analgesic use	1.00 (Reference)	-	-
Preoperative NSAID drug use	0.94	0.84-1.05	0.244
Preoperative analgesic (Non-NSAID) drug use	1.25	0.58-2.68	0.571
Type 2 diabetes	1.26	1.04-1.52	0.021
Hypertension	0.90	0.80-1.02	0.101
Operative time (min)	1.00	1.00-1.00	<0.001 [†]
TXA use	0.43	0.39-0.48	<0.001 [†]
Drain use	2.48	2.21-2.78	<0.001 [†]
Intraoperative blood loss (mL)	1.00	1.00-1.00	<0.001 [†]

Abbreviations: OR, odds ratio; CI, confidential interval; BMI, body mass index; ASA, American Society of Anesthesiologists; Hb, hemoglobin; min, minute; NSAIDs, nonsteroidal anti-inflammatory drugs; TXA, tranexamic acid. *p* value calculated using multivariate logistic regression;

[†]Results were significant after Bonferroni correction.