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Factors associated with high hidden blood loss in patients undergoing primary total knee arthroplasty for osteoarthritis: a cross-sectional retrospective study of 1444 patients

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Abstract

Purpose Total knee arthroplasty (TKA) can cause significant hidden blood loss after surgery, and transfusion or erythropoietin (EPO) treatment may be required. This study aimed to identify the factors associated with blood loss in patients undergoing TKA for osteoarthritis (OA).

Methods We retrospectively enrolled 1444 OA patients undergoing primary TKA from January 2022 to June 2024. The patients were divided into two groups according to the grade of hidden blood loss. To identify the key influencing factors, we conducted a logistic regression analysis.

Results This study analyzed 1,444 primary arthroplasty cases, identifying 236 patients with high hidden blood loss (HHBL). Coronary artery disease (CAD) was significantly more prevalent in the HHBL group (15.3% vs. 9.4%, $p = 0.006$). Preoperative EPO use was higher in the low hidden blood loss (LHBL) group (21.9% vs. 9.3%, $p < 0.001$). Significant preoperative lab differences included hemoglobin, hematocrit, and platelet count. Surgical factors associated with HHBL included left knee TKA, conventional mechanical TKA (CMTKA), longer operation times, and intraoperative blood loss (IBL) > 20%. Postoperatively, the HHBL group had significantly more transfusions and longer hospital stays. Logistic regression identified CAD, platelet count, left knee surgery, CMTKA, operation time, and preoperative EPO use as significant factors influencing HHBL. These findings highlight the need for targeted strategies to manage blood loss in knee arthroplasty patients.

Conclusions This study identifies several factors associated with high hidden blood loss in patients undergoing TKA for osteoarthritis. CAD, CMTKA, prolonged operation time, left-sided surgery, lower preoperative platelet count, and lack of preoperative erythropoietin (EPO) use were significantly linked to HHBL. While these associations highlight potential targets for intervention, further prospective studies are needed to confirm causality.

Keywords Total knee arthroplasty, Osteoarthritis, Hidden blood loss, Factors

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Introduction

Total Knee Arthroplasty (TKA) is recognized as a cost-effective and durable solution for treating severe knee osteoarthritis, particularly when less invasive treatments are insufficient [1–5]. Despite its efficacy and widespread use, TKA is often complicated by significant blood loss, with volumes typically ranging from 1000 to 2000 mL [6]. Although surgical techniques have improved significantly [7], managing high blood loss after TKA remains a major concern for surgeons. Traditionally, the focus has been on managing visible perioperative blood loss, which can be directly quantified and controlled during and immediately after the surgery. However, a significant amount of blood loss, known as hidden blood loss (HBL), occurs postoperatively and presents ongoing challenges.

Introduced by Sehat et al. in 2000, the concept of HBL accounts for approximately 50% of the total calculated blood loss in TKA procedures [8, 9]. This excessive bleeding significantly contributes to postoperative anemia, often necessitating blood transfusions and extending hospital stays [10]. Additionally, patients receiving transfusions during the perioperative period face up to a 20% increase in hospital costs and a 20 to 25% longer hospitalization [11, 12]. Allogeneic blood transfusions also carry risks such as infection transmission, transfusion reactions, graft versus host disease, and immunosuppression [13]. Moreover, increased HBL is associated with more severe pain, higher risks of hematoma formation, wound infections, and diminished knee joint mobility [14].

Several factors contribute to perioperative anemia, including patient characteristics, surgical techniques, and thromboprophylaxis methods aimed at preventing venous thromboembolic events (VTEs) [15]. However, the existing results of influential factors in OA patients undergoing TKA remain controversial. The variability in hidden blood loss and the frequency of blood transfusions in primary cemented TKA are notable and influenced by a range of factors.This study seeks to delineate the primary factors that contribute to significant hidden blood loss in patients undergoing TKA for osteoarthritis.

Materials and methods

Patients and data sources

We conducted a retrospective analysis of 1444 consecutive patients diagnosed with osteoarthritis who underwent primary total knee arthroplasty in our orthopedic department from January 2022 to June 2024. The study received approval from the hospital's ethics committee, ensuring compliance with ethical standards. Data were meticulously extracted from the hospital's electronic medical records system, which verified the diagnosis of osteoarthritis and facilitated the collection of comprehensive patient data. Collected variables included: (1) Demographics: age, sex, BMI, smoking and alcohol consumption history; (2) Comorbidities and medication history: hypertension, diabetes, cerebral infarction, CAD (defined as coronary artery stenosis confirmed by prior coronary angiography), atrial fibrillation, renal disease, liver disease, varicose veins in the legs, preoperative DVT, preoperative anticoagulant, preoperative EPO; (3) Surgical: laterality, ASA grade, anaesthetic types (general, spinal, epidural, regional or combined anesthesia), technique (CMTKA/RTKA), tourniquet use and time, prosthetic type (CR, PS or others [including rotational knee system and prosthesis with stems]), operation time; (4) Laboratory test (preoperatively and in postoperative day 3): Hb, Hct, PLT, WBC, TT, APTT, PT, INR, fibrinogen, D-dimer. Patients were divided into two groups based on whether their HBL exceeded 20 percent of the calculated total blood volume. Primary endpoint: Incidence of HHBL (HBL >20% PBV). Secondary endpoints: transfusion rate, hospital stay duration.

Exclusion criteria were strictly adhered to, eliminating patients from the study if they: (1) underwent simultaneous bilateral TKA; (2) were diagnosed with inflammatory arthritis, such as spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, or systemic lupus erythematosus; (3) had incomplete hematocrit (Hct) data; (4) Pre-existing hematologic disorders; or (5) had ruptured patellar ligament postoperatively (Fig. 1).

Perioperative treatment

Preoperative and postoperative EPO, along with iron supplementation, was prescribed for patients with hemoglobin levels lower than 12.9 g/dL or 9.5g g/dL, separately. Patients on long-term anticoagulation therapy were bridged with low-molecular-weight heparin (LMWH). Those with preoperative lower limb venous thrombosis underwent a vascular surgery consultation to rule out surgical contraindications and were also treated with LMWH anticoagulation. Postoperative transfusion was considered if the hemoglobin level fell below 70 g/L or if symptoms of anemia were present, such as decreased blood pressure (<90/60 mmHg), pale lips, dizziness, weakness, and shortness of breath.

Surgical technique

All procedures were performed by experienced surgeons. Anesthesia was tailored to each patient based on the anaesthetist's evaluation, considering factors such as age, comorbidities, medical history, and surgical risk. Tourniquet application was differentiated into early inflation (before skin incision and released post-wound closure) and late inflation (before prosthesis placement and released after joint capsule closure). Tranexamic acid (TXA) was administered as a 1 g intravenous injection

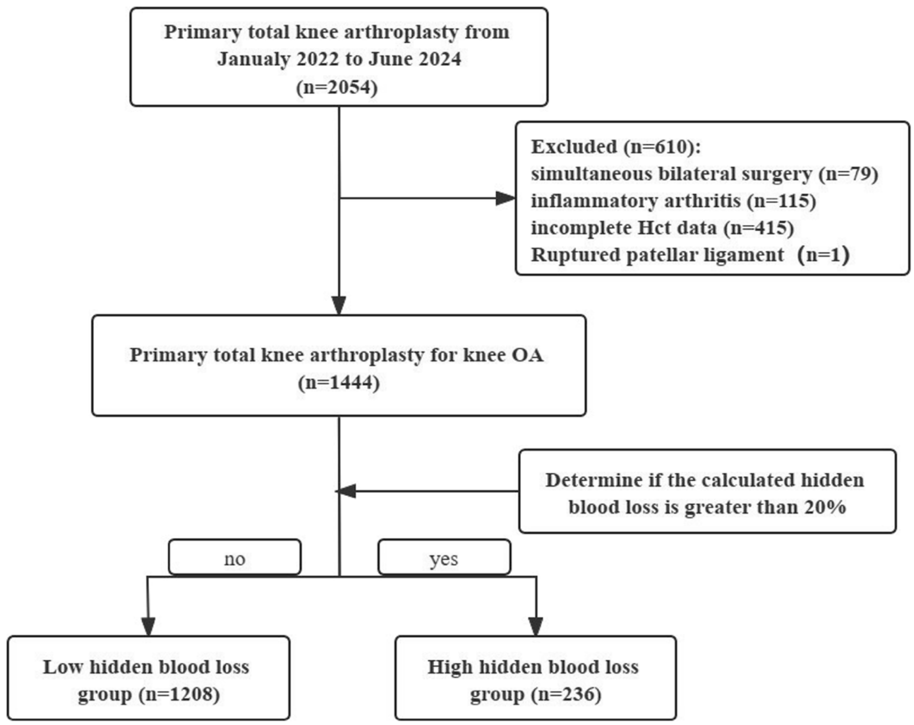

Fig. 1 Flowchart of the identification of high hidden blood loss group

30 min before the skin incision. Each patient underwent a cemented knee arthroplasty, with the type of prosthesis chosen based on the individual's joint condition and the surgeon's assessment.

An anteromedial incision was made for a medial parapatellar approach. In both CMTKA and robotic-assisted TKA (RTKA), the objective was to achieve neutral mechanical alignment. For CMTKA, femoral resection was guided by intramedullary referencing, while tibial bone resection used extramedullary referencing. Appropriate soft tissue releases were performed to balance flexion and extension gaps.

In RTKA, preoperative preparation involved comprehensive imaging with computed tomography scans to create detailed three-dimensional models of each patient's knee joint. These models informed personalized surgical plans that specified bone resection and implant placement parameters, tailored to each knee's unique anatomical features to ensure optimal implant fit and orientation. At the start of the RTKA procedure, the robotic system was calibrated, and tracking markers were placed on the patient's knee for real-time spatial tracking. The robotic system then executed precise bone cuts according to the preoperative plan, with a high degree of accuracy ensuring proper preparation of bone surfaces. Additional capsular or ligamentous releases were performed as needed. Following the osteotomy, a trial mold of the prosthesis was installed to assess knee mobility and stability. The final prosthesis was then installed, and the incision was sutured. Femoral and tibial tracers and fixation nails were removed after closing the articular capsule.

Intra-articular administration of 1g tranexamic acid was performed. Intraoperative blood loss was continuously monitored, with transfusion management handled by an anesthesiologist.

Postoperative rehabilitation

All patients received the same treatment regimen, including an intravenous injection of tranexamic acid, anti-infectives, analgesics, and anticoagulants. Postoperatively, they began weight-bearing walking exercises with a floor walker and non-weight-bearing knee flexion and extension exercises, typically starting the day after surgery. Discharge criteria included adequate pain control, knee flexion of at least 90 degrees, and independent mobility with crutches.

Calculation of hidden blood loss

Perioperative blood loss includes total blood loss (TBL), introperative blood loss (IBL), and HBL. The patient's blood volume (PBV) can be calculated using the formula of Nadler et al. [16]:

$$\text{PBV (L)} = \text{k1} \times \text{height (m)}^3 + \text{k2} \times \text{weight (kg)} + \text{k3};$$

where kl =0.3669, k2 =0.03219, k3 =0.6041 for male; and kl =0.3561, k2 =0.03308, k3 =0.1833 for female.

Gross 's formula [17] was then used to calculate total blood loss based on PBV and hematocrit drop. Hct was measured preoperatively and at 3 days postoperatively for all patients. Morning blood samples were collected to minimize diurnal variation.

$$\text{TBL} = \text{PBV} \times (\text{Hct}_{\text{preoperative}} - \text{Hct}_{\text{day 3 postoperative}}) \div \text{average Hct};$$

Average Hct was defined as the arithmetic mean of preoperative and postoperative day 3 Hct values: $(\text{Hct}_{\text{preoprative}} + \text{Hct}_{\text{day 3 postoperative}})/2$;

$$\text{HBL} = \text{TBL} - \text{IBL} + \text{postoperative transfusion volume}.$$

Statistical analysis

All data were analysed using SPSS Statistics version 26.0 (IBM, Armonk, NY, USA). Categorical variables were presented as frequencies (percentages) and continuous variables as means ± standard deviations (SD) or medians with interquartile ranges (IQR), depending on their distribution assessed by the Shapiro-Wilk test. Inter-group differences in continuous variables were evaluated using Student's t-test or Mann-Whitney U-test, depending on the type of data and whether they were normally distributed. Differences in categorical data were assessed using Pearson's chi-squared test, while Fisher's exact test was used when a significant number of cells had an expected value of less than 5. Backwards stepwise binary logistic regression was used to identify factors associated with HBL in knee OA patients undergoing TKA. Variables with $p < 0.1$ in univariate analysis were entered into backward stepwise regression (exit threshold $p > 0.05$). Variance inflation factors (VIF) <5 confirmed no multicollinearity. Model calibration was assessed via Hosmer–Lemeshow test ($p = 0.248$). Differences were considered significant when $P < 0.05$.

Results

The baseline preoperative clinical characteristics of the patients are detailed in Table 1. This study encompassed 1,444 primary arthroplasty cases, with 236 patients categorized into the HHBL group. The median age at admission was 67.0 years (IQR: 63.0, 71.0 years), and the median BMI was 27.1 kg/m^2 (IQR: 25.0, 29.5 kg/m^2). A majority of the patients, 1,097 (75.9%), were female. Smoking history was present in 6.6% of patients, and 98 (6.8%) had a history of alcohol consumption, with no significant differences between the HHBL and LHBL groups. Comorbidity history was

Table 1 Clinical baseline characteristics of the primary TKA patients

Baseline characters	Total (*n* = 1444)	LHBL (*n* = 1208)	HHBL (*n* = 236)	*p*-value
Age (years)	67.0 (63.0, 71.0)	67.0 (63.0, 71.0)	67.5 (63.0, 71.0)	0.621[a]
Female (n, %)	1097 (75.9)	925 (76.6)	172 (72.9)	0.225[b]
BMI (kg/m^2)	27.1 (25.0 29.5)	27.1 (25.0, 29.6)	27.2 (24.8, 29.4)	0.654[a]
Smoking (n, %)	95 (6.6)	79 (6.5)	16 (6.8)	0.892[b]
Alcohol drinking (n, %)	98 (6.8)	82 (6.8)	16 (6.8)	0.996[b]
Comorbidity history (n, %)				
Hypertension	799 (0.55)	661 (54.7)	138 (58.5)	0.288[b]
Diabetes	269 (18.6)	226 (18.7)	43 (18.2)	0.860[b]
Cerebral infarction	89 (6.2)	75 (6.2)	14 (5.9)	0.343[b]
CAD	149 (10.3)	113 (9.4)	36 (15.3)	0.006[b*]
Atrial fibrillation	16 (1.1)	13 (1.1)	3 (1.3)	0.736[c]
Renal disease	25 (1.7)	22 (1.8)	3 (1.3)	0.785[c]
Liver disease	15 (1.0)	12 (1.0)	3 1.3)	0.723[c]
Varicose Veins in the Legs	113 (7.8)	98 (8.1)	15 (6.4)	0.358[b]
Preoperative DVT	51 (3.5)	40 (3.3)	10 (4.2)	0.478[b]
Preoperative anticoagulant (n, %)	178 (12.3)	140 (11.6)	38 (16.1)	0.054[b]
Preoperative EPO (n, %)	186 (19.8)	264 (21.9)	22 (9.3)	< 0.001[b]

LHBL low hidden blood loss group, *HHBL* high hidden blood loss group, *BMI* body mass index, *CAD* coronary artery disease, *DVT* deep venous thrombosis, *EPO* erythropoietin

[a] Mann-Whitney U-test

[b] Pearson's chi-square test

[c] Fisher's exact test

largely similar between the groups, except for CAD, which was significantly more prevalent in the HHBL group (15.3% vs. 9.4%, $p=$ 0.006). Preoperative anticoagulant use showed a trend toward significance ($p=0.054$). Conversely, preoperative EPO use was significantly higher in the LHBL group (21.9% vs. 9.3%, $p<$ 0.001).

Table 2 The preoperative lab test of the primary TKA patients

Parameters	LHBL (*n* = 1208)	HHBL (*n* = 236)	*p*-value
Hb (g/L)	128.0 (119.0, 136.0)	130.0 (121.0, 138.0)	0.013[a]
PLT (× 10^9/L)	228.0 (191.3, 268.0)	208.0 (173.25, 247.0)	< 0.001[a]
WBC (× 10^9/L)	0.39 (0.22 to 0.75)	0.34 (0.22 to 0.64)	0.104[a]
RBC (× 10^9/L)	4.29 (3.97 to 4.57)	4.32 (4.04 to 4.60)	0.211[a]
Hct (L/L)	0.383 ± 0.038	0.389 ± 0.038	0.019[b]
TT (s)	17.0 (16.5, 17.6)	17.0 (16.3, 17.6)	0.591[a]
APTT (s)	26.9 (25.4, 28.6)	27.2 (25.7, 29.0)	0.081[a]
PT (s)	11.5 (11.1, 12.0)	11.5 (11.1, 12.0)	0.400[a]
INR	0.97 (0.94, 1.01)	0.98 (0.95, 1.02)	0.132[a]
Fibrinogen (g/L)	3.0 (2.6, 3.4)	3.0 (2.5, 3.49)	0.861[a]
D-dimer (μg/mL)	0.39 (0.22, 0.75)	0.34 (0.22, 0.64)	0.093[a]

Hb hemoglobin, *PLT* platelet, *WBC* white blood cell count, *RBC* red blood cell count, *Hct* hematocrit, *TT* thromboplastin time, *APTT* activated partial thromboplastin time, *PT* prothrombin time, *INR* international normalized ratio

[a] Mann–Whitney U-test

[b] Student t-test

Preoperative lab tests (Table 2) revealed significant differences in hemoglobin ($p=0.013$), hematocrit (Hct) ($p<0.001$), and platelet count ($p=0.019$). No significant differences were observed in WBC, RBC, TT, APTT, PT, INR, fibrinogen level, and D-dimer between the groups ($p>0.05$).

Surgical factors (Table 3) indicated that the HHBL group had a significantly higher proportion of patients undergoing left knee TKA ($p=0.009$), adopting CMTKA ($p<0.001$), experiencing longer operation times ($p=0.002$), and having IBL > 20% ($p=0.004$). Similar trends were noted for intraoperative blood loss, the ratio of intraoperative blood loss to PBV, and intraoperative transfusion rate, though these were not statistically significant ($p>0.05$). Anesthetic type, tourniquet use rate, tourniquet duration, and prosthesis type choice did not differ significantly between the groups ($p>0.05$).

Postoperative data (Table 4) showed that both the volume of HBL and its proportion relative to PBV were significantly greater in the HHBL group compared to the

Table 3 Surgical factors

Baseline characters	LHBL (*n* = 1208)	HHBL (*n* = 236)	*p*-value
Left/right knee (n, %)	579 (47.9)/629 (52.1)	135 (57.2)/101 (42.8)	0.009[a]
ASA grade ≥ 3 (n, %)	32 (2.6)	3 (1.3)	0.208[b]
Anaesthetic (n, %)			0.324[a]
General	552 (45.7)	107 (45.3)	
Spinal	15 (1.2)	5 (2.1)	
Epidural	79 (6.5)	22 (9.3)	
Regional	17 (1.4)	5 (2.1)	
Combined	545 (45.1)	97 (41.1)	
CMTKA/RTKA (n, %)	957 (79.2)/251 (20.1)	220 (93.2)/16 (6.8)	< 0.001[a]
Tourniquet use (n, %)	982 (81.3)	190 (80.5)	0.778[a]
Tourniquet time (min)	54.0 (34.0, 71.8)	55.0 (34.0, 75.8)	0.207[b]
Prosthesis type(n, %)			0.339[a]
CR	26 (2.2)	6 (2.5)	
PS	1151 (95.3)	220 (93.2)	
others	31 (2.6)	10 (4.2)	
Operation time (min)	110.0 (95.0, 126.0)	115.0 (100.0, 132.8)	0.002[b]
IBL > 20% (n, %)	163 (13.5)	49 (20.8)	0.004[a]
IBL (mL)	367.6 (150.8, 613.8)	403.8 (166.5, 716.2)	0.206[b]
IBL/PBV (%)	9.2 (3.7, 15.0)	9.5 (4.2, 17.1)	0.323[b]
Intraoperative transfusion (n, %)	69 (5.7)	18 (7.6)	0.258[a]

ASA American Society of Anesthesiologists classification, *CMTKA* conventional manual total knee arthroplasty, *RTKA* robotic-assisted total knee arthroplasty, *CR* cruciate-retaining prosthesis, *PS* posterior-stabilized prosthesis; others: including rotational knee system and prosthesis with stems; *IBL* Intraoperative blood loss, *PBV* patient's blood volume

[a] Pearson's chi-square test

[b] Mann–Whitney U-test

LHBL group ($p < 0.001$). Specifically, the median HBL was 964.4 mL (IQR: 856.1–1146.4 mL) in the HHBL group, markedly higher than the 419.1 mL (IQR: 259.6–600.8 mL) observed in the LHBL group. Similarly, the median HBL/PBV ratio was 23.7% (IQR: 21.5%–26.7%) in the HHBL group, compared to 10.5% (IQR: 6.4%–14.8%) in the LHBL group. Furthermore, patients in the HHBL group required more postoperative blood transfusions ($p < 0.001$) and experienced longer hospital stays post-surgery ($p < 0.001$). However, there were no significant differences between the groups regarding the use of post-operative anticoagulants or the incidence of symptomatic DVT.

Among 29 patients requiring postoperative transfusion, 6 patients (20.7%) met the hemoglobin threshold (< 70 g/L), while the remaining 23 (79.3%) were transfused due to symptomatic anemia despite higher Hb levels. Notably, all six patients with Hb < 70 g/L belonged to the high hidden blood loss (HHBL) group, exhibiting a substantially elevated mean HBL/PBV ratio of 33.12% compared to the overall HHBL cohort average of 23.7%

Logistic regression analysis (Table 5) identified several factors associated with high hidden blood loss in osteoarthritis patients undergoing primary knee arthroplasty: CAD (odds ratio [OR] = 1.72; 95% confidence interval [CI], 1.12 to 2.63; $p = 0.013$), platelet count (OR = 0.99; 95% CI, 0.99 to 1.00; $p < 0.001$), left knee surgery (OR = 1.44; 95% CI, 1.07 to 1.93; $p = 0.015$), CMTKA (OR = 4.48; 95% CI, 2.56 to 7.83; $p < 0.001$), operation time (OR = 1.01; 95% CI, 1.01 to 1.02; $p < 0.001$), and preoperative EPO use (OR = 0.41; 95% CI, 0.25 to 0.67; $p < 0.001$). D-dimer levels were nearly significant (OR = 0.81; 95% CI, 0.66 to 1.00; $p = 0.057$).

Discussion

With the advancement of sophisticated blood management strategies, surgeons now have greater opportunities to minimize blood loss and reduce transfusion risks [7]. TXA in particular, has gained widespread attention in recent studies for its efficacy in significantly reducing bleeding without increasing the risk of VTEs [18–21]. Despite the routine intraoperative and postoperative use of TXA for bleeding management, this study indicated that over 16.3% of patients still experienced postoperative bleeding exceeding 20% of their blood volume. This substantial bleeding led to a marked increase in postoperative blood transfusion rates and extended hospital stays for patients in the HHBL group. Consequently, these factors not only heighten the financial burden on patients but also elevate the risk of postoperative complications.

This study provides a comprehensive analysis of the factors contributing to HHBL in osteoarthritis patients undergoing TKA. Our findings underscore the complexity of managing HBL, which remains a significant challenge despite advancements in surgical techniques and perioperative care.

The results indicate that CAD is a notable risk factor for HHBL. Although CAD may not be a direct cause of increased HBL, patients with it often have a long history of anticoagulant use. It aligns with previous studies that suggest long-term anticoagulated populations

Table 4 Postoperative data

Baseline characters	LHBL ($n = 1208$)	HHBL ($n = 236$)	p-value
HBL (mL)	419.1 (259.6, 600.8)	964.4 (856.1, 1146.4)	< 0.001[b]
HBL/PBV (%)	10.5 (6.4, 14.8)	23.7 (21.5, 26.7)	< 0.001[b]
Postoperative anticoagulant (n, %)			0.115[a]
Unprescribed	61 (5.0)	12 (5.1)	
Aspirin	230 (19.0)	253 (19.7)	
Nadroparin calcium	623 (51.6)	131 (55.5)	
Fondaparinux sodium	128 (10.6)	17 (7.2)	
Rivaroxaban	37 (3.1)	2 (0.8)	
Dalteparin sodium	36 (12.9)	157 (10.3)	
Postoperative EPO (n, %)	277 (22.9)	66 (28.0)	0.096 [a]
Postoperative transfusion (n, %)	15 (1.2)	14 (5.9)	< 0.001[a]
Postoperative length of stay	4 (3, 5)	4 (3, 7)	< 0.001[b]
Postoperative symptomatic DVT (n, %)	11 (0.9)	1 (0.4)	0.703[c]

HBL hidden blood loss, *PBV* patient's blood loss, *EPO* erythropoietin, *DVT* deep venous thrombosis

[a] Pearson's chi-square test

[b] Mann-Whitney U-test

[c] Fisher's exact test

Table 5 Backwards stepwise binary logistic regression of the risk factors for HBL in patients with knee osteoarthritis involvement undergoing TKA

Characteristic	Univariable		Multivariable	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
CAD	1.74 (1.16 to 2.61)	0.007	1.72 (1.12 to 2.63)	0.013
WBC (× 10^9/L)	0.91 (0.82 to 1.00)	0.039	-	0.582
Hct (L/L)	83.28 (2.05 to 3389.10)	0.019	-	0.449
Hb (g/L)	1.02 (1.01 to 1.03)	0.004	-	0.308
PLT (× 10^9/L)	0.99 (0.99 to 1.00)	< 0.001	0.99 (0.99 to 1.00)	< 0.001
D-dimer (μg/mL)	0.76 (0.61 to 0.94)	0.011	0.81 (0.66 to 1.00)	0.057
Left knee/right knee	1.45 (1.10 to 1.92)	0.009	1.44 (1.07 to 1.93)	0.015
CMTKA/RTKA	3.61 (2.13 to 6.10)	< 0.001	4.48 (2.56 to 7.83)	< 0.001
Operation time (min)	1.01 (1.00 to 1.01)	< 0.001	1.01 (1.01 to 1.02)	< 0.001
IBL > 20%	1.68 (1.18 to 2.40)	0.004		0.306
EPO prescription	-		-	
No prescription	-	-	-	-
Preoperation	0.38 (0.23 to 0.60)	< 0.001	0.41 (0.25 to 0.67)	< 0.001
Postoperation	1.07 (0.78 to 1.48)	0.665	1.20 (0.85 to 1.68)	0.295

CAD coronary artery disease, *TKA* total arthroplasty, *OR* odd ratios, *CI* confidence interval, *WBC* white blood cell count, *Hct* hematocrit, *Hb* hemoglobin, *PLT* platelet, *CMTKA* conventional manual total knee arthroplasty, *RTKA* robotic-assisted total knee arthroplasty, *IBL* Intraoperative blood loss, *EPO* erythropoietin

undergoing joint arthroplasty are at a higher risk of bleeding [22]. A plausible mechanism could be the effect of anticoagulation on early hemostasis at the incision site, resulting in impaired wound healing and subsequent infection [23]. The higher prevalence of CAD in the HHBL group highlights the need for careful preoperative assessment to mitigate blood loss risks. Interestingly, our analysis revealed that preoperative platelet count inversely correlates with HBL, suggesting that higher platelet levels may offer a protective effect against excessive bleeding. This finding could inform preoperative optimization strategies, such as platelet augmentation, to reduce HBL. While D-dimer levels approached significance in the logistic regression analysis, they did not emerge as a definitive predictor of HBL in our cohort. This suggests that while D-dimer may reflect coagulation activity, its role in predicting HBL requires further investigation.

Another interesting finding in this study is that left knee arthroplasty significantly increased the risk of HHBL by 44% compared with right knee arthroplasty. This reminds doctors that patients should pay more attention to exercises and assistive devices that promote lower limb circulation during left knee surgery. While our observation of elevated HHBL risk in left-sided TKAs aligns with potential venous outflow obstruction mechanisms akin to May-Thurner anatomical variations, this hypothesis warrants further validation through dedicated Doppler ultrasound assessments of iliac venous hemodynamics. In anatomical variations, the left common iliac vein (LCIV) is compressed between the lower lumbar spine and the right common iliac artery (RCIA) [24, 25]. The intimal hyperplasia in the LCIV due to the shear stress on the anterior and posterior walls of the LCIV secondary to the pulsation of the overlying RCIA contributes to venous obstruction [26]. Based on this anatomical background, venous return is significantly more obstructed in the left lower limb than in the right lower limb. Notably, although symptomatic DVT incidence showed no intergroup difference (Table 4), future studies should incorporate systematic postoperative screening for both symptomatic and asymptomatic DVT events using standardized duplex ultrasonography protocols at 48-72 h and 2 weeks postoperatively.

EPO is the main hematopoietic hormone acting on progenitor red blood cells via stimulation of cell growth, differentiation, and anti-apoptosis [27]. The regression analysis reveals that the preoperative use of EPO was highly associated with LHBL, while postoperative use of the EPO did not show to have an impact. This aligns with evidence from Martina et al., who reported that preoperative iron and/or EPO supplementation effectively reduces transfusion requirements without compromising long-term outcomes [28]. The observed discrepancy suggests that preoperative EPO stimulates erythropoiesis sufficiently to partially offset perioperative blood loss, whereas postoperative initiation likely occurs too late to exert clinically meaningful hematological effects. Importantly, EPO prescriptions in this cohort were guided by baseline Hb (< 12.9 g/dL) rather than randomized allocation, introducing potential selection bias as patients with poorer hematologic profiles were more frequently treated preoperatively. Despite this limitation, this finding supports the use of EPO as part of a blood management strategy in TKA patients when patients' preoperative Hb is low.

Surgical technique and operative duration emerged as critical determinants of hidden blood loss (HBL). Our analysis revealed a 3.48-fold increased risk of high hidden blood loss (HHBL) with conventional mechanical total knee arthroplasty (CMTKA) compared to robotic-assisted TKA (RTKA). Additionally, every additional minute of operative time conferred a 1% incremental risk of HHBL. This disparity may stem from fundamental technical differences: CMTKA employs intramedullary femoral canal instrumentation, which disrupts bone marrow cavities and vascular networks, whereas RTKA utilizes small-diameter tracking pins placed in the tibia and femur, minimizing osseous and soft tissue trauma. The robotic platform's precision in osteotomy execution – guided by preoperative 3D planning – likely preserves periarticular vasculature and reduces intra-articular bleeding sources [29]. These mechanistic advantages align with Song et al.'s findings of 34% lower postoperative drainage volumes in RTKA versus CMTKA (613 mL vs 933 mL) [30]. Notably, while RTKA procedures require additional time for system calibration and registration, operative time remained an independent risk factor in multivariate analysis even after adjusting for surgical technique. This suggests that prolonged exposure to surgical stress – irrespective of technology type – exacerbates coagulopathic processes or inflammatory-mediated capillary leakage.

Limitations

Our study has several limitations that warrant careful consideration when interpreting the findings. First, as a single-center retrospective analysis, the results may be influenced by institutional practices and patient population characteristics, limiting generalizability. While we employed strict exclusion criteria, unmeasured confounders inherent to retrospective designs—such as surgeon-specific preferences, subtle variations in postoperative care, and socioeconomic factors—could introduce bias.

Second, the use of preoperative erythropoietin (EPO) was non-randomized and based on preoperative Hb <12.9 g/dL. This introduces potential selection bias, as patients receiving EPO likely had lower baseline hemoglobin levels, which may confound the observed association between EPO and reduced hidden blood loss (HBL). Although we adjusted for preoperative hemoglobin in analyses, residual confounding cannot be ruled out. Future randomized controlled trials are needed to validate the causal effect of EPO on HBL mitigation.

Third, heterogeneity in thrombosis prophylaxis protocols represents another limitation. While all patients received chemical thrombosis prophylaxis, variations in dosing, timing, and duration across surgeons were not systematically recorded. Such heterogeneity could influence bleeding risk and HBL outcomes, underscoring the need for standardized anticoagulation regimens in future studies.

Fourth, postoperative rehabilitation protocols, including early mobilization and knee range-of-motion exercises, were not quantitatively assessed. Prior studies suggest that different postoperative limb positions and range of motion is known to be associated with the effects of blood loss [31]. Future prospective studies with larger, more diverse populations are warranted to validate these results and explore additional factors influencing HBL. The lack of granular data on postoperative activity levels limits our ability to evaluate this potential relationship.

Lastly, anatomical factors such as venous compression syndromes (e.g., May-Thurner anatomy) were not directly assessed, despite their theoretical relevance to left-sided HBL. While we hypothesize that left knee surgery may impair venous return, imaging confirmation of iliac vein compression was unavailable. Future prospective studies incorporating vascular imaging could clarify this mechanism.

Despite these limitations, our findings highlight critical modifiable factors in HBL management. We advocate for multicenter prospective cohorts with standardized protocols for EPO administration, anticoagulation, and rehabilitation to validate these associations and refine perioperative strategies.

Conclusion

This study identifies several factors statistically associated with high hidden blood loss (HHBL) in patients undergoing total knee arthroplasty (TKA) for osteoarthritis. CAD, conventional mechanical TKA, longer operative time, left-sided surgery, preoperative PLT, and preoperative EPO use were significantly correlated with HHBL. These findings suggest that tailored preoperative optimization—such as addressing platelet levels, CAD management, and selective EPO administration—combined with minimally invasive techniques like robotic-assisted TKA, may mitigate HHBL risks. However, the observed associations do not imply direct causation, and further prospective studies are needed to validate these relationships.

Abbreviations

TKA	Total knee arthroplasty
EPO	Erythropoietin
OA	Osteoarthritis
HHBL	High hidden blood loss
LHBL	Low hidden blood loss
CMTKA	Conventional mechanical TKA
CAD	Coronary artery disease
HBL	Hidden blood loss
VTEs	Venous thromboembolic events
BMI	Body mass index
ASA	American Society of Anesthesiologists
Hct	Hematocrit
LMWH	Low-molecular-weight heparin
TXA	Tranexamic acid
RTKA	Robotic-assisted TKA
TBL	Total blood loss
IBL	Intraoperative blood loss
PBV	Patient's blood volume
SD	Standard deviations
IQR	Medians with interquartile ranges
LCIV	Left common iliac vein
RCIA	Right common iliac artery

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Clinical trial number
Not applicable.

Authors' contributions
DT and FJ designed the study and performed data collection and validation. DT and XC performed data analysis. XC and LYJ interpreted the results. DT and HLB carried out the writing and editing. Final approval of the version to be submitted: CJY and FJ. Project guarantor: CJY and FJ. The authors read and approved the final version of the manuscript. The last two authors (CJY and FJ) contributed equally to this work and were both listed as corresponding authors.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of the General Hospital of the People's Liberation Army and in accordance with the 1964 Declaration of Helsinki. Written informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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