CLINICAL ARTICLE

Effect of an Elevated Preoperative International Normalized Ratio on Transfusion and Complications in Primary Total Hip Arthroplasty with the Enhanced Recovery after Surgery Protocol

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Objective: To verify whether an elevated preoperative international normalized ratio (INR) increases transfusion and complications independently in primary total hip arthroplasty (THA) with the management of an enhanced recovery after surgery (EARS) protocol.

Methods: We retrospectively reviewed the database of adults who underwent primary THA between 2014 and 2018 by the same surgeon. A total of 552 patients were assigned into three groups by preoperative INR class: INR ≤ 0.9, 0.9 < INR < 1.0, and INR ≥ 1.0. We regarded transfusion within 90 days during the same hospitalization as the primary outcome. We also included perioperative blood loss, maximum Hb drop, postoperative anaemia requiring medicine, and length of hospital stay (LOS) during the same hospitalization in the study. Complications and reoperation at 90 days and mortality at 90 days and 12 months were also included in the study. Univariable analyses were utilized to compare baselines and outcomes among the three groups. Multivariate logistic regressions were used to adjust for differences at baseline among the groups.

Results: All patients had an INR < 1.5 preoperatively and were managed with the ERAS protocol. Among them, 93 (16.8%) patients had INR ≤ 0.9, 268 (48.6%) patients had 0.9 < INR < 1.0, and 191 (34.6%) patients had INR ≥ 1.0. In the univariable analyses, as the INR increased, the transfusion rates increased from 1.08% for INR ≤ 0.9, to 1.12% for 0.9 < INR < 1.0 and to 5.76% for INR ≥ 1.0 ($P < 0.05$). The overall complication rate increased from 10.8% for INR ≤ 0.9, to 16.4% for 0.9 < INR < 1.0, and to 22.5% for INR ≥ 1.0 ($P < 0.05$). The length of stay (LOS) in the INR ≥ 1.0 group was 5.7 ± 2.2 days, which was significantly longer than that in the INR ≤ 0.9 group (4.7 ± 1.6 days, $P = 0.000$) and 0.9 < INR < 1.0 group (5.1 ± 2.0 days, $P = 0.007$). No statistical significance was detected among the groups regarding blood loss, maximum Hb drop, or the incidence of postoperative anaemia that required medicine. There was no significant difference in reoperation or mortality among the groups. When controlling for demographic and comorbidity characteristics, there was no statistically significant difference in the odds of transfusion during the same hospitalization or overall complications at 90 days among the groups ($P > 0.05$).

Conclusions: Elevated preoperative INR cannot increase transfusion or complication rates independently in primary THA with the management of the ERAS protocol. With the improvement in the ERAS protocol and the use of tranexamic acid (TXA), an INR < 1.5 is still a conventional safe threshold for THA surgery.

Key words: Enhanced recovery after surgery; International normalized ratio; Total hip arthroplasty; Tranexamic acid

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Introduction

Total hip arthroplasty (THA) improves the quality of life of patients with end-stage hip disease[1]. With the aging population and the prevalence of obesity[2], more than 500,000 primary THAs in 2018 were performed in the United States[3], and more than 100,000 were performed in the United Kingdom in 2019[4]. In the long run, THA surgery is a cost-saving healthcare intervention compared with non-operated patients[5].

THA is associated with excessive perioperative blood loss and a high need for transfusion[6–8]. The reported transfusion rate was as high as 29.8% in California from 2006 to 2011[9]. Blood transfusion is associated with many complications, such as haemolytic transfusion reactions, transfusion-associated circulatory overload, and transfusion-related acute lung injury[10–12]. Transfusion during THA surgery may increase the risk of wound complications, infection, and deep vein thrombosis (DVT) prolong the length of hospital stay (LOS), and increase mortality[13–16]. Over the years, efforts in blood management during THA surgery have been made to minimize the blood loss and transfusion rate, such as tranexamic acid (TXA)[17,18]. Furthermore, some risk factors for blood transfusion have been detected, such as low preoperative haemoglobin (Hb), prolonged operation time, tourniquet use, and drain use[19,20]. Recently, the theory of enhanced recovery after surgery (ERAS) has been widely used in joint surgery and was introduced by Professor Henrik Kehlet in 1997[21,22]. The ERAS program recommends decreasing surgical trauma and stress response by a series of techniques, which were proven by evidence-based medicine[23]. Management with the ERAS protocol reduces the transfusion rate, complication rate, and LOS in joint arthroplasty[23]. Although blood transfusions continued to decline in primary THA surgery from 2010 to 2015, the transfusion rate was as high as 7.1% in 2015 in the United States[24]. At present, it is still necessary to explore and understand the risk factors for blood transfusion.

During the surgical procedure, the activated coagulation system can avoid uncontrolled blood loss[25]. It is essential to maintain the balance of coagulation function. If the coagulation function is insufficient, it leads to haemorrhagic diseases. In contrast, if the coagulation function is too strong, it leads to thrombotic disorders[26,27]. After adding thromboplastin and calcium to citrated plasma, the time in seconds for plasma to coagulate is the prothrombin time (PT), which is widely used to display extrinsic coagulation function[28]. However, inter-device variations in the PT make it difficult to compare among different institutions[29]. The international normalized ratio (INR) refers to the ratio of prothrombin time to the normal prothrombin time[30] and is regarded as an ideal method for judging the anticoagulation effect[31]. It overcomes the variability among different laboratories by thromboplastin sensitivity[32]. Among the patients using warfarin, the INR was kept between the therapeutic range of 2.0 and 3.0[33]. A preoperative INR target <1.5 is suggested by the guidelines[34]. The INR is widely used in predicting mortality and bleeding in some diseases. Rudasill *et al.* found that the INR showed important value in predicting mortality and bleeding in end-stage liver disease[34]. Patients who underwent endarterectomy with high preoperative INR (≥1.5) exhibited higher 90-day mortality than low INR patients (<1.5)[35]. In another study on managing heart failure with nonvalvular atrial fibrillation, abnormal INR also showed higher independent risks of mortality[36].

Some previous studies agreed that elevated INR values have a strong association with the risk of bleeding[37,38]. A retrospective study found that patients with an INR ≥ 1.3 had a higher transfusion rate in victims of abusive head trauma[39]. An elevated INR is also associated with increased complications after hand surgery[40]. A retrospective study of more than 20,000 cases recently proved that INR > 1.25 was tightly associated with bleeding, infection, and mortality in total knee arthroplasty[41]. The same author conducted another similar retrospective study in THA and found that an elevated INR increased bleeding and mortality[42].

The evidence for the INR in predicting perioperative bleeding, complications, and mortality is still low with the management of the ERAS protocol. With the widespread use of TXA in joint surgery[17,18], it is necessary to re-evaluate the predictive value of the INR. The purpose of this retrospective study was to verify whether an elevated preoperative INR increases transfusion and complications independently in primary THA with the management of the ERAS protocol.

Methods

Inclusion and Exclusion Criteria for the Study Population

This retrospective study was approved by the Ethics Committee of West China Hospital of Sichuan University (No. 20120268), and written informed consent was obtained from each participant. We retrospectively identified a database of adults who underwent unilateral THA between 15 October 2014 and 14 October 2018, by the same experienced senior surgeon (B.S.). The same ERAS protocol managed all patients. All patients received the same general anesthesia, posterolateral approach, and usage of TXA during the surgery. The inclusion criteria were as follows: (i) adult patients (≥18 years of age); (ii) underwent unilateral primary THA in our hospital; (iii) patients with enough relevant preoperative laboratory data; and (iv) all the laboratory data were collected within 3 days preoperatively. The exclusion criteria were as follows: (i) bilateral THA during the same hospitalization; (ii) patients with previous hip septic arthritis; (iii) revision operation; (iv) multiple fractures; (v) patients without adequate data; and (vi) patients with hematologic disease.

ERAS Protocol

All patients received the same preoperative education and physical exercise after admission. Patients were encouraged to consume adequate high-protein food. Once diagnosed,

anaemia and hypoproteinaemia before surgery needed to be treated. The haemoglobin ≥120 g/L for males and ≥ 110 g/L for females were regarded as cured. Hypoproteinaemia was cured once the serum albumin ≥35 g/L. Surgery for patients who had abnormal laboratory tests, including elevated inflammatory factors, coagulation abnormalities (INR >1.5), and severe comorbidity, was re-assessed. Multimodal methods were utilized to manage perioperative patients' sleep and pain. THA surgeries were performed by the posterolateral approach under general anaesthesia. Perioperative blood loss was controlled by a series of methods comprising TXA and control blood pressure during operation. TXA was routinely administered preoperatively with intravenous dose (15 mg/kg) in all the cases, and it was administered again intravenously if the surgery time exceeded 2 hours. All drains were removed within 24 hours postoperatively. Antibiotic and DVT prophylaxis were used postoperatively. All patients were allowed to walk with or without crutches on the second day after surgery.

Study Design

All the cases were divided into three groups by preoperative INR class: INR ≤ 0.9, 0.9 < INR < 1.0, and INR ≥ 1.0. We obtained relevant in-hospital data by checking medical records in our hospital system. Patients were followed up 3 months after the specific surgery to obtain their complications, reoperation, and mortality data after discharge. Twelve months later, patients were followed up again to obtain their mortality data.

Outcome Measures

Transfusion Rate

Transfusion rate was defined as the percentage of patients who received allogeneic blood transfusion during or after surgery according to medical records. To treat anaemia and improve the oxygen-carrying capacity of the blood, allogeneic red blood cell transfusion is commonly used during the perioperative period[43]. According to the perioperative transfusion protocol provided by the Chinese Ministry of Health, we set haemoglobin <70 g/L or 70–100 g/L with symptoms as a transfusion trigger[44]. Blood transfusion is associated with excessive costs[11]. Besides, transfusion may increase the risk of complications such as transfusion reactions and postoperative infection[10–12,16].

Perioperative Blood Loss

According to medical records, perioperative blood loss was defined as the blood loss volume of patients during the perioperative period, calculated by the formulas described by Gross with preoperative haematocrit and the lowest postoperative haematocrit during hospitalization[45,46]. Excessive blood loss may lead to anemia and blood transfusions[46].

Maximum Hb Drop

Maximum Hb drop was defined as the difference between preoperative Hb and lowest postoperative Hb during hospitalization[46,47]. All the measures of hemoglobin were based on medical records. A drastically reduced Hb also lead to anemia and result in blood transfusions[46].

Postoperative Anaemia Requiring Medicine

Postoperative anaemia requiring medicine was defined as the percentage of patients who received medicine to treat anaemia after surgery according to medical records. We set Hb <100 g/L as a trigger to use medicine for postoperative anaemia. Anaemia is associated with prolonged LOS and increased blood transfusion rate, thus, should be treated[48].

Length of Hospital Stay

Length of hospital stay (LOS) means the number of nights spent in the hospital after THA surgery according to medical records.

Complication Rate Within 90 days

The complication rate within 90 days was defined as the percentage of patients who experienced any complications within 90 days after the THA. Complications at any level were included in our study, such as urinary tract infection (UTI), renal failure, stroke, cardiovascular accident, pneumonia, septic shock, pulmonary embolism (PE), DVT, superficial infection, deep infection, dislocation, fracture, muscular vein thrombosis, subcutaneous ecchymosis, haematoma, wound healing delay, etc. All the complication data were obtained from the medical records and confirmed with the patients during the follow-up period.

Reoperation Rate Within 90 days

Reoperation within 90 days was defined as the percentage of patients who underwent reoperation for any reason within 90 days after the THA. All the reoperation data were obtained from the medical records and confirmed during the follow-up period.

The Mortality Rate at 90 days and 12 months

The mortality at 90 days was defined as the percentage of patients who died for any reason within 90 days after the THA. The mortality at 12 months was defined as the percentage of patients who died for any reason within 12 months after the THA. All the mortality data were obtained from the medical records and confirmed during the follow-up period.

Statistical Analysis

Continuous variables are presented as the mean with the standard deviation or the median with the interquartile range. Categorical variables are presented as the number of patients (percentage). We analyzed continuous variables by one-way ANOVA with Tukey's post hoc test and categorical variables by the chi-square test or Fisher's test. We utilized multivariate logistic regressions to evaluate the predictive value of the INR for transfusion and complications. We used the independent variables with $P < 0.1$ in the regression model for adjustment. Regressions were adjusted for age, sex, body mass index (BMI), American Society of

Anesthesiologists (ASA) class, bacteriuria, cardiac pacemaker, preoperative Hb, haematocrit, WBC count, and serum albumin. In all the comparisons, $P < 0.05$ was considered statistically significant. All statistical analyses were performed by SPSS (version 26; IBM, Chicago, IL, USA).

Results

Demographic Characteristics and Comorbidities

From 15 October 2014 to 14 October 2018, 589 cases were screened for eligibility. Twenty-one cases were excluded: 14 failed to meet the inclusion criteria, and seven lacked adequate preoperative data. We allocated the remaining patients into three groups by the INR class. Three, eight, and five patients were lost to follow-up in the three groups. There was no significant difference in the distribution of the lost-to-follow-up patients among the groups. Finally, 552 cases were included in our study (Fig. 1).

All the patients had an INR < 1.5, which was considered a conventional safe threshold. Among all the patients, 93 (16.8%) had INR ≤ 0.9, 268 (48.6%) had 0.9 < INR < 1.0, and 191 (34.6%) had INR ≥ 1.0. As the INR increased among the groups, the ASA class increased gradually (P <0.05). The preoperative haematocrit decreased from 0.415 ± 0.037 L/L for INR ≤ 0.9 and 0.406 ± 0.041 L/L for 0.9 < INR < 1.0 to 0.398 ± 0.045 L/L for INR ≥ 1.0 ($P < 0.05$). Serum albumin also decreased from 44.8 ± 4.7 g/L for INR≤0.9, to 43.8 ± 4.1 g/L for 0.9 < INR < 1.0, and to 42.9 ± 4.5 g/L for INR ≥ 1.0 ($P < 0.05$). The patients with cardiac pacemakers were different among the groups: 0.0% for INR ≤ 0.9, 0.0% for 0.9 < INR < 1.0, and 2.1% for INR ≥ 1.0 ($P < 0.05$). There were no significant differences between the INR groups in age, sex, BMI, comorbidities except cardiac pacemakers, preoperative erythrocyte sedimentation rate (ESR), platelet count, WBC count, nor D-dimer (Table 1).

Outcomes of Univariate Analysis

Transfusion Rate

As presented in Table 2, as the INR increased, the transfusion rates increased from 1.12% for 0.9 < INR < 1.0 to 5.76% for INR ≥ 1.0 ($P = 0.004$). There was no statistically significant difference in the transfusion rate in group A *vs* group B or group A *vs* group C ($P = 1.000$ and $P = 0.112$, respectively).

Perioperative Blood Loss

The blood loss increased from 895.6 ± 378.3 ml for INR ≤ 0.9, to 915.9 ± 353.2 mL for 0.9 < INR < 1.0 to 978.7 ± 390.3 mL for INR ≥ 1.0, but there were no significant differences detected ($P = 0.892$, $P = 0.180$, and $P = 0.174$, respectively) (Table 2).

Maximum Hb Drop

The maximum Hb drop increased from 25.7 ± 10.5 g/L for INR ≤ 0.9, to 26.3 ± 9.9 g/L for 0.9 < INR < 1.0 to 27.3 ± 9.9 g/L for INR ≥ 1.0, which were not significantly different among the three groups ($P = 0.857$, $P = 0.406$, and $P = 0.553$, respectively) (Table 2).

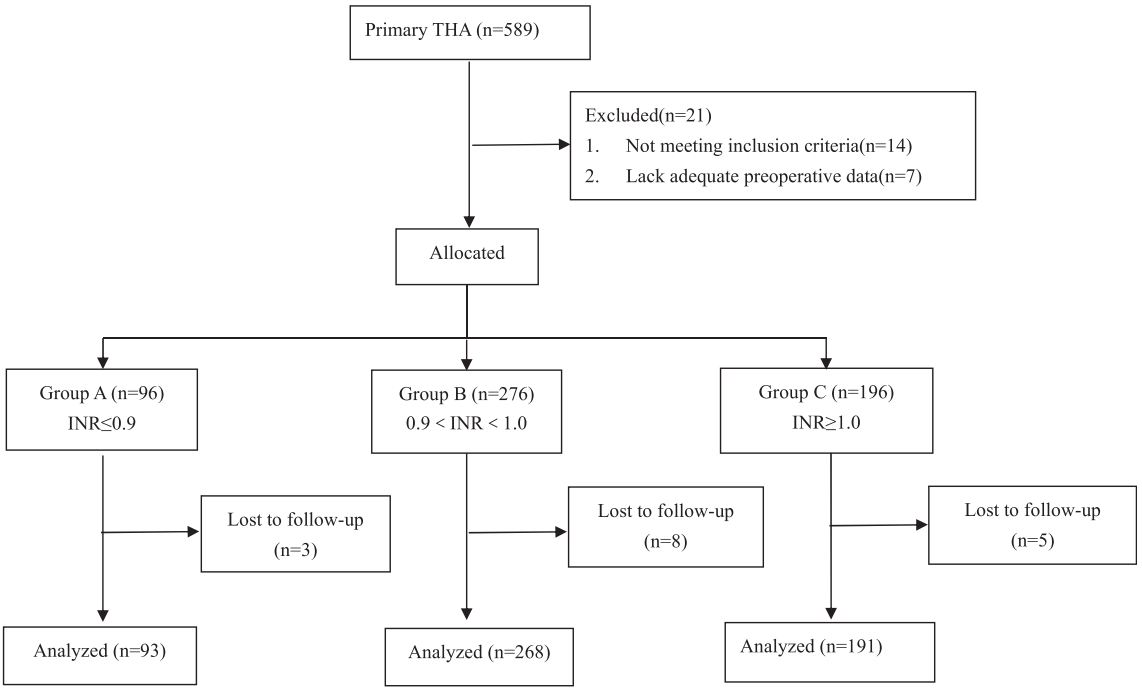

Fig 1 Flow diagram of cases involved. THA, total hip arthroplasty; INR, international normalized ratio.

TABLE 1 Demographic characteristics and comorbidities for cases of THA classificated by INR

Demographics	INR ≤ 0.9 (n = 93)	0.9 < INR < 1.0 (n = 268)	INR ≥ 1.0 (n = 191)	Statistic	*P* Value
Age* (years)	55.1 ± 11.6	54.8 ± 11.4	56.1 ± 12.4	$F = 0.785$	0.457
Sex†				$\chi^2 = 0.643$	0.721
Male	41 (44.1%)	118 (44.0%)	91 (47.6%)		
Female	52 (55.9%)	150 (56.0%)	100 (52.4%)		
BMI*‡ (kg/m^2)	23.4 ± 2.9	23.4 ± 3.3	23.4 ± 3.5	$F = 0.024$	0.976
ASA class†				$\chi^2 = 17.264$	0.006
1	18 (19.4%)	26 (9.7%)	13 (6.8%)		
2	56 (60.2%)	176 (65.7%)	109 (57.1%)		
3	18 (19.4%)	62 (23.1%)	64 (33.5%)		
4	1 (1.1%)	4 (1.5%)	5 (2.6%)		
Comorbidities					
Hypertension†	21 (22.6%)	60 (22.4%)	47 (24.6%)	$\chi^2 = 0.332$	0.847
Diabetes mellitus†	4 (4.3%)	14 (5.2%)	11 (5.8%)	$\chi^2 = 0.230$	0.904
COPD†	0 (0.0%)	5 (1.9%)	6 (3.1%)	$\chi^2 = 2.856$	0.227
Heart disease†	2 (2.2%)	5 (1.9%)	5 (2.6%)	$\chi^2 = 0.449$	0.925
Arrhythmia†	3 (3.2%)	19 (7.1%)	16 (8.4%)	$\chi^2 = 2.588$	0.265
Cancer†	2 (2.2%)	5 (1.9%)	2 (1.0%)	$\chi^2 = 0.842$	0.735
Renal insufficiency†	0 (0.0%)	4 (1.5%)	3 (1.6%)	$\chi^2 = 1.060$	0.685
SLE†	3 (3.2%)	8 (3.0%)	7 (3.7%)	$\chi^2 = 0.269$	0.948
AS†	1 (1.1%)	9 (3.4%)	7 (3.7%)	$\chi^2 = 1.351$	0.541
Venous thrombosis†	1 (1.1%)	5 (1.9%)	4 (2.1%)	$\chi^2 = 0.295$	1.000
Bacteriuria†	4 (4.3%)	22 (8.2%)	23 (12.0%)	$\chi^2 = 4.920$	0.085
Cardiac pacemaker†	0 (0.0%)	0 (0.0%)	4 (2.1%)	$\chi^2 = 5.663$	0.030
Preoperative laboratory					
Hemoglobin* (g/L)	136.1 ± 14.5	133.6 ± 15.3	131.4 ± 16.9	$F = 2.849$	0.059
Hematocrit* (L/L)	0.415 ± 0.037	0.406 ± 0.041	0.398 ± 0.045	$F = 5.086$	0.006
ESR* (mm/h)	25.16 ± 18.3	25.0 ± 16.8	25.6 ± 20.3	$F = 0.060$	0.942
Platelet count* (×10^9)	185.5 ± 60.4	184.6 ± 62.3	178.8 ± 62.0	$F = 0.597$	0.551
WBC count* (×10^9)	6.1 ± 1.6	6.2 ± 2.1	5.8 ± 1.8	$F = 2.589$	0.076
D-Dimer* (mg/L)	0.73 ± 1.0	0.73 ± 0.9	0.9 ± 1.0	$F = 1.162$	0.314
Serum albumin*(g/L)	44.8 ± 4.7	43.8 ± 4.1	42.9 ± 4.5	$F = 5.761$	0.003

AS, ankylosing spondylitis; ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary diseases; SLE, systemic lupus erythematosus; WBC, white blood cell.; * Continuous variables are exhibited as the mean and the standard deviation, analysed by the one-way ANOVA.; † Categorical variables are exhibited as the number of cases (the percentage), analysed by the Pearson chi-square test or the Fisher exact test.; ‡ Among the BMI, 11 cases in group B and two cases in group C did not acquire BMI data.

Postoperative Anaemia Requiring Medicine

The incidence of anaemia requiring medicine also increased from 16.1% for INR ≤ 0.9, to 20.9% for 0.9 < INR < 1.0 to 23.6% for INR ≥ 1.0, without statistical significance ($P = 0.319$, $P = 0.150$, and $P = 0.497$, respectively) (Table 2).

Length of Hospital Stay

As presented in Table 2, the LOS for INR ≥ 1.0 was 5.7 ± 2.2 days, which was statistically longer than that for INR ≤ 0.9 (4.7 ± 1.6 days, $P = 0.000$) and 0.9 < INR < 1.0 (5.1 ± 2.0 days, $P = 0.007$) (Fig. 2).

TABLE 2 Clinical outcomes for cases of THA classificated by INR

Outcomes	Group A INR ≤ 0.9 (n = 93)	Group B 0.9 < INR < 1.0 (n = 268)	Group C INR ≥ 1.0 (n = 191)	Statistic A *vs* B *vs* C	*P* value A *vs* B *vs* C	*P* value A *vs* B	*P* value A *vs* C	*P* value B *vs* C
Transfusion rate†	1 (1.08%)	3 (1.12%)	11 (5.76%)	$\chi^2 = 8.788$	0.008	1.000	0.112	0.004
Blood loss* (ml)	895.6 ± 378.3	915.9 ± 353.2	978.7 ± 390.3	$\chi^2 = 2.209$	0.111	0.892	0.180	0.174
Maximum Hb drop* (g/L)	25.7 ± 10.5	26.3 ± 9.9	27.3 ± 9.9	$\chi^2 = 0.964$	0.382	0.857	0.406	0.553
Anemia requiring medication†	15 (16.1%)	56 (20.9%)	45 (23.6%)	$\chi^2 = 2.085$	0.353	0.319	0.150	0.497
Length of stay* (days)	4.7 ± 1.6	5.1 ± 2.0	5.7 ± 2.2	$F = 8.354$	0.000	0.243	0.000	0.007

* Continuous variables are exhibited as the mean and the standard deviation, analysed by the one-way ANOVA with Tukey's post hoc test.; † Categorical variables are exhibited as the number of cases (percentage), analysed by the Pearson chi-square test or Fisher test.

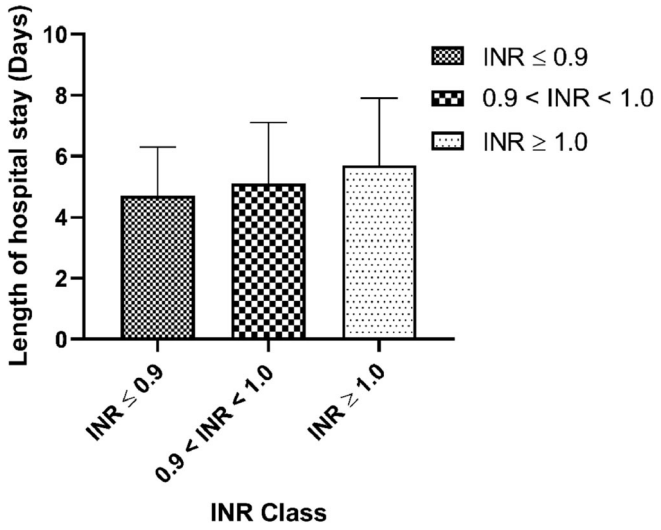

Fig 2 Outcomes of the length of hospital stay. The histogram showed that compared with patients for INR ≤ 0.9 and 0.9 < INR < 1.0, patients for INR ≥ 1.0 led to a longer length of hospital stay. INR, international normalized ratio.

Complication Rate Within 90 days

Among all the patients, 10 (10.8%) had complications with INR ≤ 0.9, 44 (16.4%) with 0.9 < INR < 1.0, and 43 (22.5%) with INR ≥ 1.0 postoperatively. There was a significant difference in complications between INR ≤ 0.9 and INR ≥ 1.0 ($P = 0.017$). Continuously increasing trends were observed among the groups regarding the incidence of cardiovascular accidents, superficial infection, muscular vein thrombosis, subcutaneous ecchymosis, and wound healing delay without statistical significance. We also found no significant differences among groups regarding UTI, renal failure, stroke, pneumonia, septic shock, pulmonary embolism, DVT, deep infection, dislocation, fracture, haematoma, and wound healing delay ($P > 0.05$) (Table 3).

Reoperation Rate at 90 days

As presented in Table 3, two (0.7%) patients with 0.9 < INR < 1.0 and four patients (2.1%) with INR ≥ 1.0 underwent reoperation within 90 days postoperatively. There was no significant difference in the reoperation rate at 90 days among the groups ($P = 0.272$).

Mortality Rate at 90 days and 12 months

No patients died within 90 days postoperatively. Two patients (1.0%) with INR≥1.0 died within 12 months postoperatively. There was no significant difference in mortality at 90 days or 12 months among the groups (Table 3).

Outcomes of Multivariate Logistic Regressions

After adjusting for independent variables with $P < 0.1$ in the regression model, we found no significant difference in transfusion (Table 4) or complications at 90 days (Table 5) among the three groups. We adjusted for age, sex, BMI, ASA

TABLE 3 Complication, reoperation and mortality outcomes classificated by INR

Outcomes	Group A INR ≤ 0.9 (n = 93)	Group B 0.9 < INR < 1 (n = 268)	Group C INR ≥ 1 (n = 191)	Statistic A *vs* B *vs* C	*P* value A *vs* B *vs* C	*P* value A *vs* B	*P* value A *vs* C	*P* value B *vs* C
Any Complication†	10 (10.8%)	44 (16.4%)	43 (22.5%)	$\chi^2 = 6.452$	0.040	0.187	0.017	0.101
Urinary tract infection†	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA	NA	NA	NA	NA
Renal failure†	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA	NA	NA	NA	NA
Stroke†	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA	NA	NA	NA	NA
Cardiovascular accident†	0 (0.0%)	1 (0.4%)	4 (2.1%)	$\chi^2 = 3.432$	0.157	1.000	0.307	0.166
Pneumonia†	0 (0.0%)	0 (0.0%)	1 (0.5%)	$\chi^2 = 2.015$	0.514	NA	1.000	0.416
Stroke†	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA	NA	NA	NA	NA
Septic shock†	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA	NA	NA	NA	NA
Pulmonary embolism†	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA	NA	NA	NA	NA
DVT†	1 (1.1%)	0 (0.0%)	0 (0.0%)	$\chi^2 = 2.871$	0.168	0.258	0.327	NA
Superficial infection†	0 (0.0%)	5 (1.9%)	5 (2.6%)	$\chi^2 = 2.117$	0.358	0.334	0.176	0.748
Deep infection†	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA	NA	NA	NA	NA
Dislocation†	1 (1.1%)	1 (0.4%)	3 (1.6%)	$\chi^2 = 2.067$	0.321	0.449	1.000	0.312
Fracture†	0 (0.0%)	0 (0.0%)	2 (1%)	$\chi^2 = 2.762$	0.264	NA	1.000	0.173
Muscular vein thrombosis†	2 (2.2%)	11 (4.1%)	10 (5.2%)	$\chi^2 = 1.496$	0.488	0.528	0.348	0.568
Subcutaneous ecchymosis†	6 (6.5%)	21 (7.8%)	17 (8.9%)	$\chi^2 = 0.524$	0.777	0.662	0.478	0.683
Hematoma†	0 (0.0%)	3 (1.1%)	2 (1.0%)	$\chi^2 = 0.660$	0.856	0.572	1.000	1.000
Wound healing delay†	1 (1.1%)	3 (1.1%)	4 (2.1%)	$\chi^2 = 0.861$	0.718	1.000	1.000	0.457
Reoperation in 90 days†	0 (0.0%)	2 (0.7%)	4 (2.1%)	$\chi^2 = 2.308$	0.272	1.000	0.307	0.239
Mortality in 90 days†	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA	NA	NA	NA	NA
Mortality in 12 months	0 (0.0%)	0 (0.0%)	2 (1.0%)	$\chi^2 = 2.762$	0.264	NA	1.000	0.173

DVT, deep venous thrombosis.; † Categorical variables are exhibited as the number of cases (the percentage), analysed by the Pearson chi-square test or Fisher test.

TABLE 4 Outcomes of multivariate logistic regressions on transfusion rate in 90 days

	Transfusion rate	
Factor	OR (95% CI)	*P* value
Unadjusted		
INR class		
INR ≤ 0.9	Reference	-
0.9 < INR < 1	1.04 (0.11 to 10.14)	0.972
INR ≥ 1	5.62 (0.72 to 44.22)	0.101
Adjusted*		
INR class		
INR ≤ 0.9	Reference	-
0.9 < INR < 1	0.34 (0.03 to 3.90)	0.384
INR ≥ 1	1.11 (0.11 to 11.00)	0.929

* Adjusted for age, sex, BMI, ASA class, bacteriuria, cardiac pacemakers, preoperative haemoglobin, haematocrit, WBC count, and serum albumin.

TABLE 5 Outcomes of multivariate logistic regressions on complication in 90 days

	Complication rate in 90 days	
Factor	OR (95% CI)	*P* value
Unadjusted		
INR class		
INR ≤ 0.9	Reference	-
0.9 < INR < 1	1.63 (0.79 to 3.39)	0.190
INR ≥ 1	2.41 (1.15 to 5.05)	0.020
Adjusted*		
INR class		
INR ≤ 0.9	Reference	-
0.9 < INR < 1	1.43 (0.67 to 3.02)	0.353
INR ≥ 1	1.93 (0.89 to 4.19)	0.096

* Adjusted for age, sex, BMI, ASA class, bacteriuria, cardiac pacemakers, preoperative haemoglobin, haematocrit, WBC count, and serum albumin.

class, bacteriuria, cardiac pacemakers, preoperative haemoglobin, haematocrit, WBC count, and serum albumin.

Discussion

Preoperative elevated INR has been confirmed to increase bleeding, complications, and mortality in some other diseases[34–40]. Measuring INR before joint surgery was a standard pattern in our institution. However, few studies have explored the relationship between elevated INR and postoperative outcomes in joint replacement, especially with the management of ERAS protocols. In this retrospective study of 552 cases, we found that the transfusion and complication rate did not increase independently with an elevated INR in primary THA with management by the ERAS protocol.

In the INR ≥ 1.0 group, more patients had ASA classes 3 and 4, with statistical significance ($P = 0.005$). Knol *et al.* also found that the proportion of high ASA classes in patients with INR ≥ 1.8 was higher than that in patients with INR < 0.8 (69% and 48.7%, respectively, $P = 0.036$)[49]. Demographic data showed that patients with elevated INR values had lower preoperative haematocrit and serum albumin. Rudasill *et al.* detected similar baseline data in THA and TKA surgery[41,42]. There were no significant differences in other demographic and comorbidity characteristics among the groups.

This was the first study, to the best of our knowledge, that found the transfusion and complication rates did not increase independently along with an elevated INR in primary THA with management of the ERAS protocol. Our findings differed from a recent study of Rudasill *et al.*[42], who retrospectively analyzed 17,567 patients by the National Surgical Quality Improvement Program (NAQIP). He and his team found an increased bleeding risk with INR 1.25 to <1.5 (OR, 1.55 [95% CI 1.26 to 1.92]) and an increased risk of mortality with INR ≥ 1.5 (OR, 2.69 [95% CI, 1.07 to 6.76]) compared with INR < 1.0. Several reasons account for these differences. First, Rudasill *et al.*[42] focused their study on patients between 2005 and 2016, while we only included patients between 2014 and 2018. With the recent improvement in the ERAS protocol and the use of TXA, our institute has significantly reduced transfusions, complications, and mortality in total joint arthroplasty[18,50–52]. Rudasill *et al.* did not describe the perioperative management protocol, which was essential for the outcome of THA. Since 2012, almost all patients who underwent TKA or THA surgery in our institution have received TXA during the perioperative period. Our average transfusion rate of all cases was 2.7%, which was much lower than that of Rudasill *et al.* (15.5%). The mortality within 90 days of Rudasill *et al.*'s study was 0.8%. No patients (0.0%) died in 3 months, and two patients (0.3%) died in 12 months postoperatively in our study. A 10-year national database from the UK also showed that postoperative complications were reduced year by year in THA, although the levels of comorbidity were elevated[53]. Second, some THA-related complications, such as dislocation, fracture, wound healing delay, and vein thrombosis, were not included by Rudasill *et al.* The debate about INR safety thresholds has been ongoing for a long time. Some previous studies agreed that high INR values strongly correlate with the risk of bleeding in heart valve replacement and head trauma[37–39]. However, others observed that an elevated INR did not increase bleeding risk in chest tube placement or hand surgery[54,55]. In our study, we found that with management by the ERAS protocol in THA surgery, the influence of an elevated INR above the conventional safety threshold (<1.5) on blood transfusion and complications was relatively small.

With the INR elevated by the class step, the LOS increased more gradually than INR ≤ 0.9 with statistical significance. Similar results can be found in other studies[41,42,56]. We identified some minor complications in our study, such

as muscular vein thrombosis and subcutaneous ecchymosis[57–61]. Increasing trends can be detected in the incidence of cardiovascular accidents, superficial infections, muscular vein thrombosis, subcutaneous ecchymosis, and wound healing delay. However, there were no significant difference in those growing trends. We detected no significant difference in reoperation, mortality at 90 days, or mortality at 12 months.

With the progress of ERAS theory, studies have shown a reduction in LOS, maintenance of satisfactory postoperative outcomes, and decreased readmission rates[62]. Although only a few perioperative interventions were associated with reduced complications, greater use of ERAS protocol was associated with a decrease in postoperative complications[63]. Ding *et al.* found that managing comorbidities aggressively with ERAS protocol minimized the influence of comorbidities on LOS[64]. We also found elevated preoperative INR could not increase transfusion or complication rates independently with the ERAS protocol.

There are some limitations to the current study. First, this was a retrospective study, and there may be some natural bias regarding the data. Second, 16 patients were lost to follow-up, but there were no significant differences in the distribution of the lost-to-follow-up rates among the groups (3.1%, 2.9%, and 2.6%, respectively). We believe our lost-to-follow-up rate was acceptable for these parameters. Third, some patients failed to report adequate information because of forgetting, which may lower the complication rate. However, we obtained most postoperative outcome data during hospitalization. Other postoperative outcomes mainly included major complications, reoperation, and mortality, which were unlikely to be forgotten by patients and their families. Therefore, we did not think those limitations would severely affect the results.

Conclusions

In conclusion, the transfusion and complication rates did not increase independently along with an elevated INR in primary THA at the conventional safety threshold (<1.5). With the management of the ERAS protocol, INR < 1.5 was still a conventional safety threshold for THA surgery.

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All authors have approved this study for publication.

Authors' Contributions

The following authors designed the study (BS), collected the data (LBP, JFZ), analysed the data (LBP, YGW), wrote the initial drafts (LBP), and ensured the accuracy of the data and analyses (BS, JY, YZ). All authors read and approved the manuscript.

Authorship Declarations

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of West China Hospital of Sichuan University (No. 20120268). Written informed consent was obtained from each patient included in the study.

Consent for Publication

Not applicable.

Availability of Data and Material

All data and materials are contained within the manuscript.

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