Perioperative red blood cell infusion and deep vein thrombosis in patients with femoral and pelvic fractures: A propensity score matching

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Research article

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Abstract

Background: The relationship between perioperative red blood cell（RBC）infusion and deep vein thrombosis(DVT) has not been determined.

Objectives: To analyze the time-event relationship between perioperative RBC infusion and DVT in patients with femoral and pelvic fractures after adjusting for confounding factors and to provide reference for optimizing DVT risk factors.

Methods: The clinical data of 569 patients with femoral and pelvic fractures who received surgical treatment from May 2018 to December 2019 were retrospectively analyzed.Propensity score matching (PSM) was performed on 20 covariates of DVT. With the formation or progression of DVT after RBC infusion as the end point, the time-event relationship between perioperative RBC infusion and DVT in patients was analyzed by binary Logistic regression.

Results: After 1:1 PSM of 569 patients included in this study, 126 patients were in the transfusion group and the non-transfusion group, respectively.Before PSM (P=0.023, OR=1.496 [95%CI,1.058-2.115]), perioperative RBC infusion was associated with DVT formation for femoral and pelvic fractures.This conclusion was still obtained after PSM (P=0.038,OR=1.728, 95%CI=(1.031,2.896)). The risk of DVT in patients with RBC infusion of 2-4U and >4U is 1.833 and 2.667 times that of ≤2U, respectively. Excluding patients who received preoperative RBC infusion and had DVT formation or progression prior to transfusion, there were still differences in perioperative RBC infusion between non-DVT group and DVT group (P=0.037, OR=2.231 [95% CI ,1.049-4.745]).

Conclusion: Perioperative RBC infusion is the cause of DVT in patients with femoral and pelvic fractures, and the risk of DVT is positively correlated with the amount of RBC infusion.

1. Introduction

Most patients with bone trauma have high blood coagulation at the same time[1], trauma and surgical damage to the vascular endothelium, long-term immobilization and edema of the surrounding tissues cause blood flow stasis, which is a high-risk group of DVT. Zhang's prospective study of patients with lower extremity fractures who received anticoagulant treatment during the perioperative period found that the incidence of DVT before, after and one month after surgery was 35%, 55%, and 40%, respectively[2]. At present, more active DVT prevention and treatment has not significantly reduced the incidence of DVT in patients with bone trauma. We are still exploring optimized risk factors for DVT, among which studies on the correlation between blood transfusion and perioperative DVT involve pediatrics[3], obstetrics [4], bariatric surgery [5], hernia repair [6], abdominal laparoscopic surgery[7], etc. However, the correlation between perioperative RBC infusion and DVT has not yet been concluded, and even contradictory conclusions have appeared. It is reported that the RBC infusion rate of patients undergoing total knee arthroplasty is 10-20% [8,9]. Patients with severe bone trauma suffer from traumatic blood loss before surgery, and face the risk of bleeding during and after surgery, and the perioperative RBC infusion rate is not low. It is necessary to study the correlation between RBC infusion and DVT in this special group of patients.

Most of the current research aims to analyze the correlation between perioperative RBC infusion and DVT, but they have not further considered the time-event relationship between the two, and cannot explain whether there is a causal relationship. In this study, PSM was used to control confounders related to DVT, and the formation or progression of DVT after RBC infusion was taken as the end point to further analyze the possible causal relationship between RBC infusion and DVT during the perioperative period. Studies on blood transfusion and DVT in patients with current bone trauma also mostly focus on surgical types such as total joint replacement patients[9,10]. In this study, patients with femoral and pelvic fractures were included in the study, and more attention was paid to the correlation between transfusion and DVT in different bone trauma types.

2. Materials And Methods

2.1 Research objects

Retrospective analysis was performed on patients undergoing surgery for femoral and pelvic fractures in our hospital from May 2018 to December 2019. Inclusion criteria: 1. Traumatic fracture; 2. Age > 18 years old; 3. Complete clinical data. Exclusion criteria: 1. Complicated blood system diseases or coagulation dysfunction; 2.A history of long-term use of anticoagulants; 3. Pregnancy; 4. Patients with severe diseases of liver, kidney, heart, brain and other important organs cannot tolerate surgery; 5. Old thrombus history. This study has been approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (2019-277) and the World Health Organization International Clinical Trial Registry (ChiCTR2000035103).

2.2 Research methods

Clinical data of the patients were collected, and the patients were divided into non-DVT group and DVT group according to the results of preoperative and postoperative deep vein Doppler ultrasound examination of both lower limbs. DVT group was defined as the development of new postoperative or preoperative thrombus after surgery. Retrospectively analyzed the association between perioperative RBC infusion (from 72 h preoperatively to 72 h postoperatively) and DVT in patients with femoral and pelvic fractures. Perioperative RBC infusion is further divided into four categories: (1) No transfusion; (2) Transfusion only before surgery; (3) Transfusion only during or after surgery; (4) Preoperative/intraoperative/postoperative blood transfusion . After controlling for confounders by PSM, if perioperative RBC infusion was associated with the occurrence of DVT, the formation or progression of DVT after RBC infusion was taken as the end point of the event to further explore the causal relationship between the two.

2.3 Data collection

Clinical data of patients were queried through electronic medical record system and surgical anesthesia system. Preoperative and postoperative pulsed Doppler ultrasonography was performed on both lower limbs using C5-1 linear probe and IU22 system (Philips ATL, Bothwell, WA, USA). Positive criteria for DVT include venous incompressibility, intravascular filling defect, and Doppler signal loss. The formation or progression of perioperative DVT was the endpoint event. The main variables in this study were the time and amount of red blood cell transfusion. The covariates that may be associated with DVT: gender, age, Body mass Index (BMI), smoking history, drinking history and other basic information.Diabetes mellitus, hypertension, coronary heart disease, hyperlipidemia, liver disease, kidney disease, lung disease, malignant tumor, hypoproteinemia, anemia, ASA grade and other complications. Preoperative waiting time (time from trauma to surgery), operative time, tranexamic acid, anticoagulant therapy.

2.4 Statistical methods

SPSS 26.0 software was used for statistical analysis.Chi-square test or Fisher's exact probability method was used for counting data, and the results were expressed as percentage (%) to analyze the covariates associated with DVT.

To control the influence of confounding factors, PSM was used to build a Logistic model, with perioperative RBC infusion as the dependent variable and DVT related variable as the covariable. 0.01 was used as caliper value to match the transfusion group and the non-transfusion group in a ratio of 1:1. The matching effect of PSM was evaluated by the standardized difference method, and the standardized difference value d was calculated. If $d < 0.1$, the matching effect was judged to be good.

After matching, the two groups of data were analyzed by binary Logistic regression, and the adjusted odds ratio (OR value) and 95% confidence interval (95%CI) were calculated to evaluate the correlation between perioperative RBC infusion and DVT. $P < 0.05$ was considered statistically significant.

3. Results

From May 2018 to December 2019, a total of 905 patients underwent lower extremity traumatic fracture surgery in our hospital, of whom 67.51% (611/905) were patients with femoral and pelvic fractures. According to the inclusion and exclusion criteria, 569 patients (93.13%) were included in the study. There were 417 males and 152 females. The mean age was 69.6±19.1 years (20-112 years). With 0.01 as caliper value and 20 factors such as gender, BMI, smoking history, alcohol consumption history, diabetes mellitus, hypertension, coronary heart disease, hyperlipidemia, liver disease, kidney disease, lung disease, malignant tumor, hypoproteinemia, anemia, ASA grade as covariates, 126 cases were matched in the transfusion group and the non-transfusion group at a ratio of 1:1.

3.1 Comparison of DVT correlative covariates between two groups before and after PSM

Before PSM, there were 360 cases (63.27%) in the non-transfusion group and 209 cases (36.73%) in the transfusion group. There were no significant differences in gender, BMI, smoking history, drinking history, diabetes mellitus, hypertension, coronary heart disease, hyperlipidemia, liver disease, kidney disease, lung disease, malignant tumor and anticoagulant therapy between the two groups ($P > 0.05$). However, there were statistically significant differences between the two groups in age (P=0.002), hypoproteinemia (P=0.000), anemia (P=0.000), ASA grade (P=0.010), operation time (P=0.000), time from trauma to operation (P=0.003), tranexamic acid (P=0.024).

After caliper matching of data between groups by PSM method, 126 cases were found in each group. There was no statistical significance in the above 20 DVT-related covariates between the two groups ($P > 0.05$), indicating that the data of the two groups were balanced and comparable, as shown in Table 1.

3.2 Equilibrium of the two covariables before and after matching

Standardization difference of each covariable between the two groups before and after matching was calculated (d). Standardization difference of 14 covariables including age, sex, lung disease and hypoproteinemia between the two groups (D) was matched (> 0.1).After matching, the D values of 19 covariables except hyperlipidemia (d=0.102) were all < 0.1, indicating that PSM had a good matching effect, as shown in Figure 1.

3.3 Perioperative erythrocyte infusion rate of patients before and after PSM

Among the 569 patients, 36.73% (209/569) received perioperative RBC infusion (from preoperative 72 h to postoperative 72 h), and the rates of preoperative, intraoperative and postoperative RBC infusionwere 8.44% (48/569),29.70% (169/569) and 13.88% (79/569), respectively. After matching, preoperative, intraoperative and postoperative RBC infusion rates of 252 patients were 8.33%, 40.48% and 18.25%, respectively, as shown in Figure 2.

3.4 Correlation analysis of perioperative red blood cell transfusion and DVT formation before and after PSM

Before PSM (Model 1), perioperative RBC infusion was associated with the formation of DVT for femoral and pelvic fractures in 569 patients (P=0.023). After PSM (Model 2), perioperative RBC infusion was an independent risk factor for the development of DVT in femoral and pelvic fractures (P=0.038), and the risk of DVT in patients with PSM was 1.728 times higher than in patients without RBC infusion. In terms of the timing of transfusion, only intraoperative or postoperative RBC infusion was associated with DVT formation, as shown in Figure 3.

Further analysis of the total intraoperative or postoperative RBC infusion volume of the patients showed that the perioperative risk of DVT was positively correlated with the transfusion volume. The risk of DVT in patients with RBC infusion of 2-4U and >4U were 1.833 and 2.667 times higher than ≤2U, respectively, as shown in Table 2.

3.5 Analysis of the time-event relationship between perioperative red blood cell transfusion and DVT

In conclusion, perioperative RBC infusion can increase the risk of DVT for femoral and pelvic fractures, and the risk is positively correlated with the amount of transfusion. To explore the causal relationship between perioperative RBC infusion and the occurrence or progression of DVT, as shown in the time-event relationship (Model 3). Among the 252 patients after PSM, we further excluded those who received blood transfusion within 72 hours before surgery (21 cases) and those whose DVT occurred or progressed before blood transfusion (5 cases). A total of 226 patients were included, as shown in Figure 4. The study found that there was still a difference in perioperative RBC infusion between the DVT group and the non-DVT group (P=0.037, OR=2.231 [95%CI,1.049-4.745]), as shown in Figure 3.

4. Discussion

Bone trauma patients are at high risk of DVT.A large number of literatures have reported the risk factors related to DVT in patients with perioperative bone trauma, such as lower extremity and pelvic fracture, high energy trauma, Glasgow score, prolonged preoperative waiting time, long operative time, advanced age, obesity, and history of malignant tumor[11-13]. The relationship between perioperative RBC infusion and the risk of DVT is controversial.Jackson, Hart, Frisch et al reported that perioperative erythrocyte infusion does not significantly increase the incidence of venous thromboembolism (VTE) after total joint replacement[14-16].Rothstein,Helm,Jiang, Goel, Dillon et al. proved that perioperative RBC infusion would increase the risk of VTE[3,6,8,17-19]. In recent years, studies on the correlation between the two have drawn contradictory conclusions. It is necessary to conduct PSM analysis of perioperative RBC infusion and DVT in patients with femoral and pelvic fractures. Before PSM, we found that perioperative RBC infusion was associated with the formation of DVT in patients with femoral and pelvic fractures (P=0.023, OR=1.496 [95%CI,1.058-2.115]). Further PSM analysis for recognized and possible risk factors associated with DVT and sensitivity analysis for confounding variables showed that the association remained (P=0.038, OR=1.728 [95%CI,1.031-2.896]). Moreover, the risk of DVT in patients with femoral and pelvic fractures who received RBC infusion during perioperative period was 1.728 times higher than that in patients who did not receive RBC infusion. Patients receivingRBC infusion may have one or more DVT risk factors, which may be the reason for the association found in pre-matching data analysis. Patients receiving RBC infusion may have one or more DVT risk factors, which may explain the association found in previous PSM data analysis. However, we still reached the same conclusion after controlling the confounders of DVT with PSM, which further demonstrated the independence of correlation between the two.

Although we and some researchers have confirmed that perioperative RBC infusion can increase the risk of DVT in patients undergoing surgery. Previous studies did not consider the time-event relationship between transfusion time and DVT events for the two events of RBC infusion and perioperative DVT occurrence or progression. Because of the omission of this detail, even the conclusion that perioperative RBC infusion is related to DVT does not prove a causal relationship between the two. For example, some patients who received RBC infusion before surgery have DVT after surgery, even if there is no RBC infusion before surgery, it may not be possible to avoid the occurrence of postoperative DVT. Some patients may have DVT prior to transfusion. In order to actually consider the time-event relationship between RBC infusion and the occurrence of DVT during the perioperative period, we take the formation of red blood cells or the progression of DVT as the end point of the event. After controlling for confounders based on PSM, a total of 26 patients were excluded from the above two groups, and it was found that there was still a difference in perioperative RBC infusion between the DVT group and the non-DVT group (P=0.037, OR=2.231 [95%CI,1.049-4.745]). This proves that perioperative RBC infusion is the cause of DVT formation. However, the time-events of both perioperative RBC infusion and DVT have not been reported in previous studies. Perioperative RBC infusion will increase the risk of DVT in patients undergoing surgery, which is considered to be related to the following aspects: RBC infusion can increase blood viscosity and change local hemorheology, causing erythrocyte aggregation [20]. The increase in the number of red blood cells will lead to platelet aggregation [21]. The stored red blood cells may cause blood storage damage [22], releasing free hemoglobin and particles, which react and clear nitric oxide, causing vasoconstriction and endothelial injury[23,24]. In addition, most patients with bone trauma are in a state of hypercoagulation and hyperinflammation [1], and blood transfusion can induce inflammation, which may further lead to the formation of postoperative thrombus in patients [25]. In terms of transfusion timing, we divided perioperative erythrocyte transfusion into four categories :(1) no transfusion;(2) transfusion only before surgery;(3) Only intraoperative or postoperative blood transfusion;(4) Pre/intra/postoperative blood transfusion. This study found that only intraoperative or postoperative erythrocyte infusion was associated with the occurrence of DVT (P=0.023, OR=1.870 [95%CI,1.092-3.202]), and only preoperative blood transfusion was not associated with DVT (P=0.411). However, the number of preoperative blood transfusion cases was small, and whether preoperative blood transfusion is related to DVT remains to be further studied. We also statistically analyzed the intraoperative or postoperative RBC infusion volume of patients, and found that the risk of DVT in patients with RBC infusion 2-4U and >4U were 1.833 and 2.667 times higher than ≤2U, respectively. The previous retrospective cohort study of 1233 trauma patients by Meizoso et al. using RAP score found that blood transfusion of more than 4 units was an independent risk factor for DVT[11]. No matter how to define the transfusion volume of red blood cells, our conclusions were consistent with those of Meizoso,Goel and Dillon et al. [11,18,19]. The risk of perioperative DVT was positively correlated with the transfusion volume, which is also one of the reasons for us to more strictly control the indications of blood transfusion.

Perioperative red blood cell infusion strategy depends on the comprehensive evaluation of patients' general conditions, traumatic conditions, surgery and other factors. Our hospital usually transfuses strategy depends on the comprehensive evaluation of patients' general conditions, traumatic conditions, surgery and other factors. Our hospital usually transfuses RBC for patients with preoperative anemia, intraoperative and postoperative massive blood loss. In Song's study, perioperative, intraoperative and postoperative blood transfusion rates of total joint arthroplasty patients were 17.9%, 7.9% and 11.3%, respectively [9]. Slover reported that 15% of unilateral knee replacement patients and 45% of bilateral hip arthroplasty patients received intraoperative blood transfusion [26]. The preoperative, intraoperative and postoperative blood transfusion rates of patients with femur and pelvis fractures in our hospital were

8.44%,29.70% and 13.88%, respectively.The relatively high rate of blood transfusion may be related to the fact that most of the patients in our hospital are elderly, with many complications, and most of them are transported by subordinate hospitals without surgical control of post-traumatic bleeding. Cao,Song,Slover et al. reported that risk factors for perioperative blood transfusion in patients with bone trauma included female, older age, smaller BMI, more complications, ASA grade ≥3, preoperative anemia, prolonged operation time, more intraoperative bleeding caused by no tranexamic acid, no tourniquet, and type of operation[9,26,27]. In this study, we regarded gender, age, BMI, smoking history, drinking history, diabetes, hypertension, coronary heart disease, hyperlipidemia, liver disease, kidney disease, lung disease, malignant tumor, hypoalbuminemia, anemia, ASA classification, preoperative waiting time, trauma to the operation time, operation time, use of tranexamic acid and other 20 factors as confounding factors and we controlled for bias for these factors. Almost all of the above risk factors for perioperative blood transfusion were included in the confounding factors of this study, which also increases the reliability of the results of this study. Patients with severe bone trauma may face the risk of hemorrhagic shock caused by fracture, acute intraoperative massive hemorrhage, and postoperative hematoma formation, etc. In order to achieve adequate hemoglobin levels and maintain blood oxygen-carrying capacity, perioperative red blood cell infusion may be unavoidable. Blood transfusion may also lead to adverse consequences such as prolonged hospital stay, increased medical costs, cardiopulmonary complications, sepsis, multiple organ failure and even death [28,29]. Current guidelines emphasize preoperative evaluation of trauma patients while weighing the risks and benefits of blood transfusion, and the use of adjuvant agents such as antifibrinolytic drugs to limit perioperative bleeding and secondary complications [30,31]. Due to the simultaneous risk of bleeding and thrombosis, the American guidelines for perioperative blood transfusion and adjuvant therapy in anesthesiology refer to patients' preoperative preparation including discontinuation or alteration of anticoagulant therapy [30]. Due to the high risk of sustained or recurrent bleeding, the need for surgery and other reasons, some patients with bone trauma usually delay or discontinue anticoagulation therapy, or even do not start anticoagulation. For example, patients with severe multiple injuries combined with active bleeding, postoperative bleeding or even the need for reoperation to control bleeding, and patients with multiple injuries are planned to undergo multiple surgical treatment in the near future. The strategy of perioperative blood transfusion and anticoagulant therapy is important whether there is a risk of bleeding, thrombosis, or both. Minimizing the time from admission to surgery, using non-transfusion substitutes such as iron to improve preoperative hemoglobin levels, optimizing surgical methods and improving surgical skills to limit intraoperative bleeding may reduce unnecessary blood transfusion. Considering the correlation between blood transfusion and DVT, especially for patients with bone trauma combined with DVT risk factors, we may need to more strictly grasp the indications of blood transfusion, and at the same time, we should strengthen the screening and prevention of DVT for such patients receiving blood transfusion.

The formation of DVT is a complex process, which is affected by many unknown factors. Compared with most previous studies on the risk factors of perioperative DVT in patients with bone trauma, this study used PSM and Logistics regression analysis to explore the correlation between perioperative red blood cell infusion and DVT in patients with femoral and pelvic fractures, reducing the confusion bias in the study. This achieved a balanced distribution of covariates between the case group and the control group to achieve a similar effect to prospective randomized controlled trials [32]. In addition, two types of patients who received preoperative blood transfusion and those whose DVT occurred or progressed before blood transfusion were excluded in this study. Our aim was to explore the time-event relationship between perioperative blood transfusion and DVT, and also to confirm the causal relationship between the two. This has not been reported in previous studies. Although the adjusted covariates in this study included age, gender, lung disease, preoperative anemia, etc., PSM greatly improved the covariate equilibrium between the two groups, but this study also had some limitations: We tried to control the influence of potential confounding variables on DVT, but there may be additional risk factors that were not included in our analysis, and these unknown confounding variables still had an impact on the study outcome. This study was a single-center retrospective study, and more multi-center prospective randomized controlled trials are needed in the future to further explore the relationship between perioperative blood transfusion and DVT.

5. Conclusion

Perioperative red blood cell infusion is the cause of DVT in patients with femoral and pelvic fractures, and the risk of DVT is positively correlated with the amount of perioperative red blood cell infusion. DVT screening and individualized prevention and treatment should be emphasized in patients with bone trauma who receive red blood cell infusion. Further studies are needed to investigate the effective prevention and treatment of perioperative reasonable blood transfusion and DVT in patients with lower limb bone trauma.

Abbreviations

red blood cell（RBC); deep vein thrombosis(DVT); Propensity score matching (PSM); Body Mass Index (BMI); American Society of Anesthesiologists(ASA); venous thromboembolism(VTE);

Declarations

Authors’ contributions

Bo Cheng and Linqin Wu contributed to the conception and design of the study. Linqin Wu contributed to the acquisition and analysis of data. Linqin Wu wrote the manuscript. The authors read and approved the final manuscript.

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Availability of data and materials

All the data will be available upon motivated request to the corresponding author of the present paper.

Ethics approval and consent to participate

This study was approved by the ethics committee of the first affiliated hospital of Chongqing Medical University. Informed consent was obtained from all the participants.

Consent for publication

Written informed consent was obtained from each patient to authorize the publication of their data.

Competing interests

The authors declare that they have no competing interests.

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Tables

Due to technical limitations, Tables 1 and 2 are only available as a download in the supplemental files section

Figures

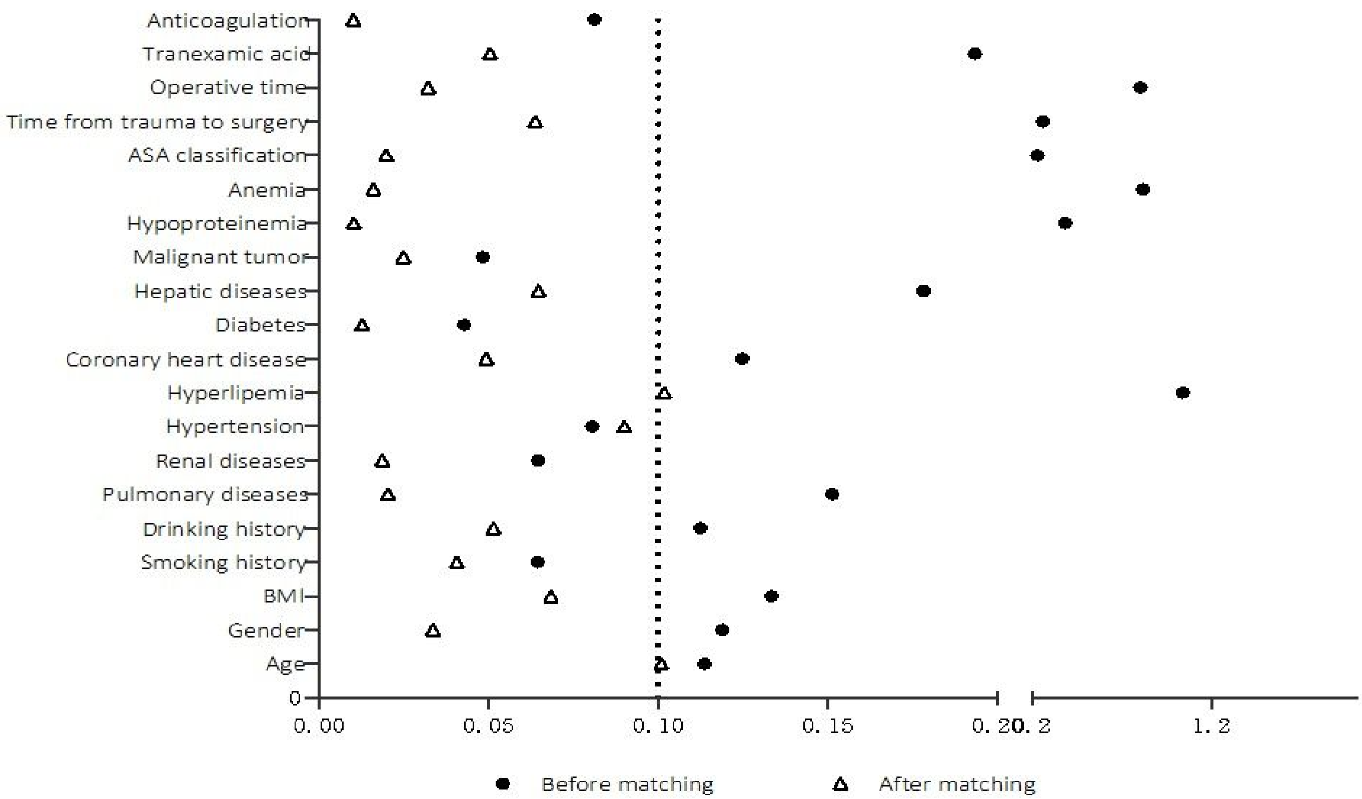

Figure 1

Variable Standardization Difference Diagram

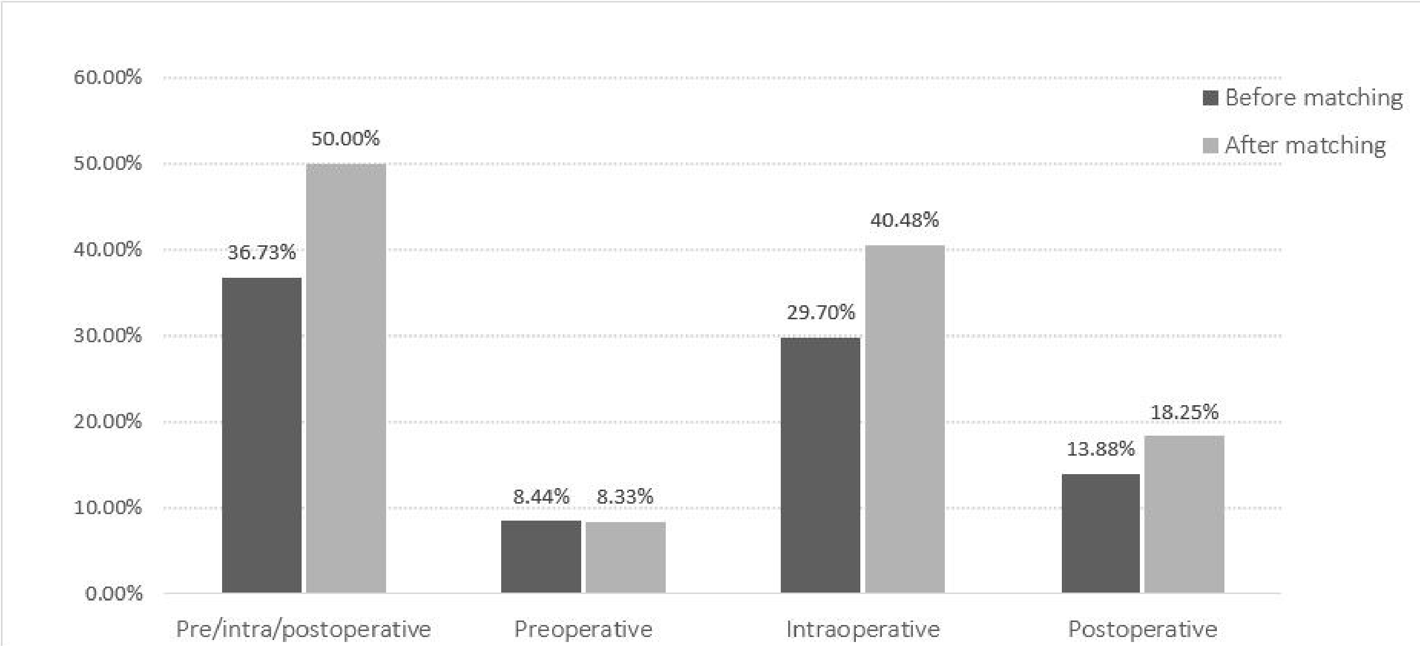

Figure 2

Perioperative red blood cell (RBC) transfusion rate before and after propensity score matching

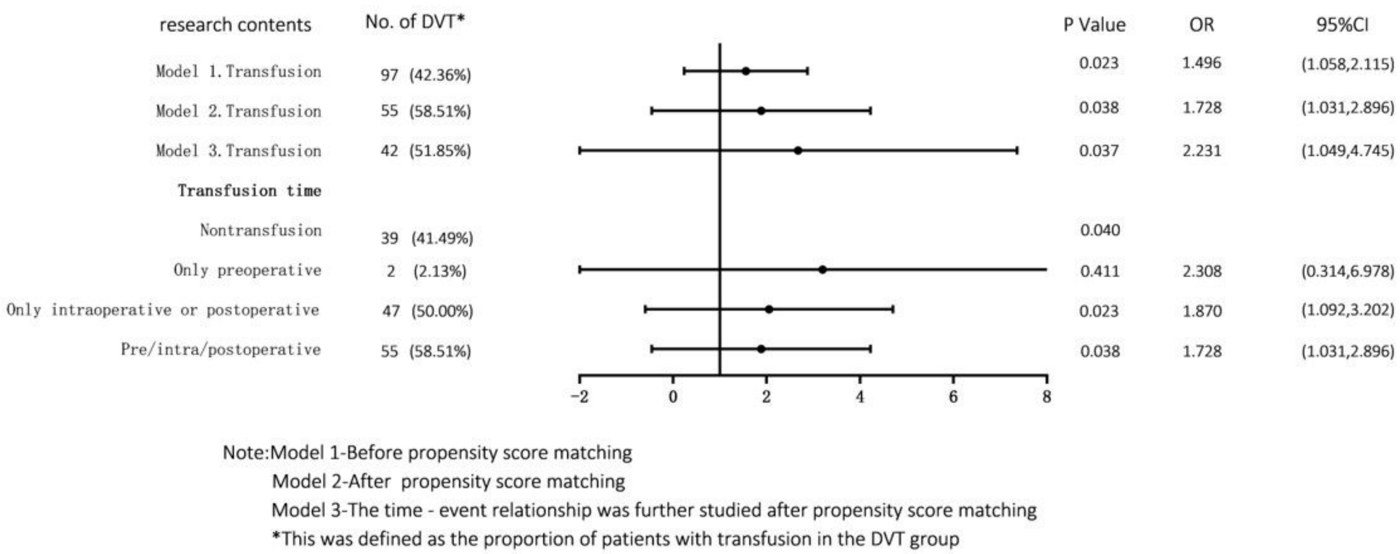

Figure 3

Binary Logistic regression analysis of perioperative RBC transfusion and DVT in patients with femoral and pelvic fractures

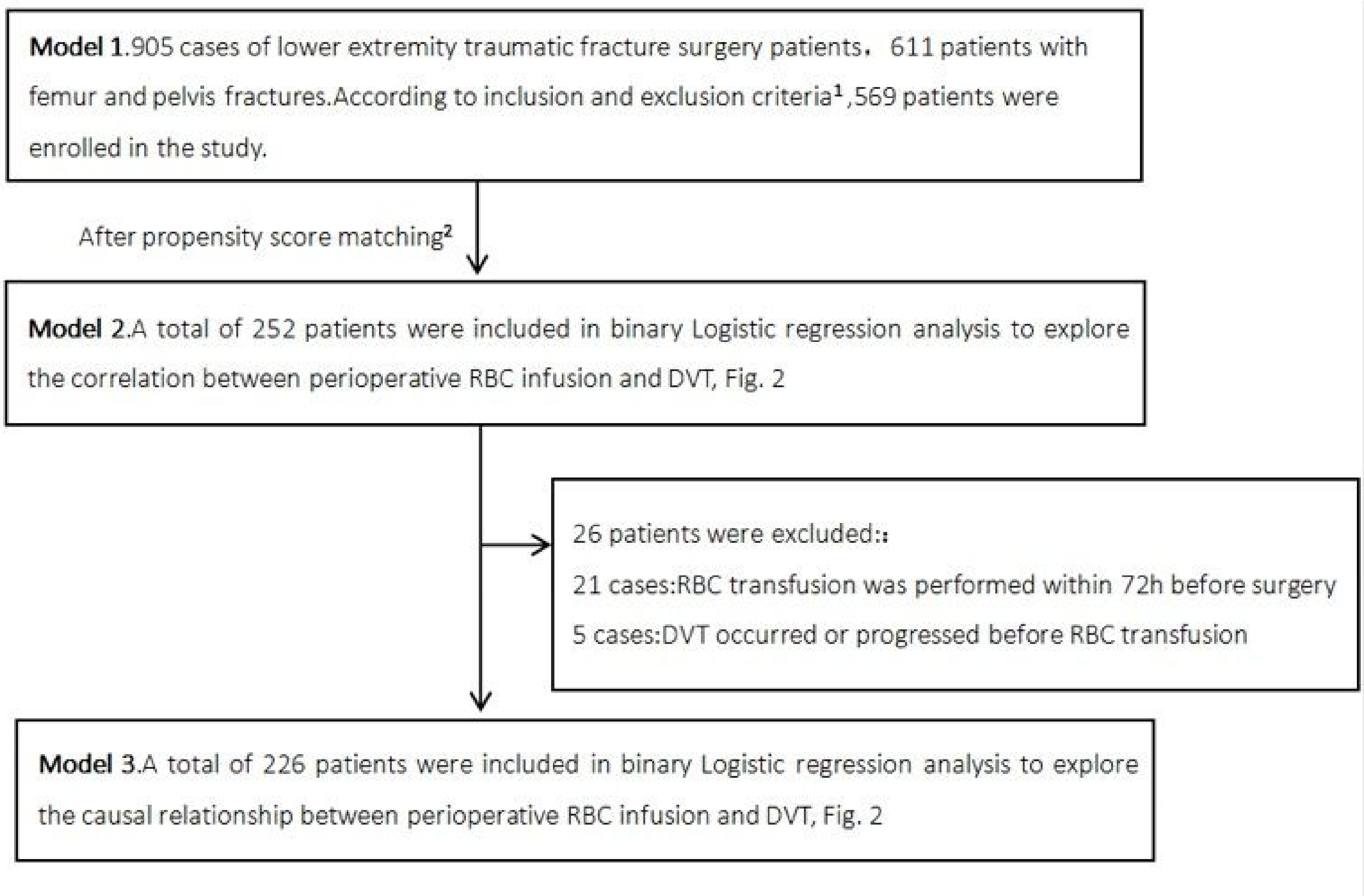

Figure 4

The Research route. Note： 1 Inclusion criteria: 1. Traumatic fracture; 2. Age> 18 years; 3. Complete clinical data. Exclusion criteria: 1. Combined with hematological diseases or coagulation dysfunction; 2. Long-term use of anticoagulant drugs; 3. Pregnancy; 4. Combined with severe liver, kidney, heart, brain and other important organ diseases cannot tolerate surgery; 5. History of old thrombosis. 2 Perioperative blood transfusion was taken as the dependent variable, DVT-related variable as the covariable, and 0.01 as the caliper value. Matching was conducted in a ratio of 1:1.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table.docx