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Evaluation of Deep Vein Thrombosis Risk Factors After Arthroscopic Posterior Cruciate Ligament Reconstruction: A Retrospective Observational Study

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Abstract

We evaluated the risk factors of deep venous thrombosis (DVT) after knee arthroscopic posterior cruciate ligament (PCL) reconstruction in patients with only PCL injury. From August 2014 to December 2020, a total of 172 patients who had accepted knee arthroscopic PCL reconstruction underwent the color Doppler ultrasound of bilateral lower-extremities deep veins on 3 days postoperatively. Based on the inspection results, patients were divided into DVT group (18 males and 8 females, mean age 43.62 years) and non-DVT group (108 males and 38 females, mean age 33.96 years). The potential associations of DVT risk and age, gender, body mass index (BMI), diabetes, hypertension, smoking and other factors were analyzed. An old age (OR = 1.090; 95% CI = 1.025-1.158; $P = 0.006$), a high BMI (OR = 1.509; 95% CI = 1.181-1.929; $P = 0.001$) and an increased post-surgery D-dimer (OR = 5.034; 95% CI = 2.091-12,117; $P \leq 0.001$) value were significantly associated with an elevated DVT risk after knee arthroscopic PCL reconstruction. Increased age, BMI, and postoperative D-dimer were risk factors of DVT following knee arthroscopic PCL reconstruction in patients with only PCL injury.

Keywords

posterior cruciate ligament, deep venous thrombosis, risk factors

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Introduction

As a common complication of major orthopedic surgery such as total knee and hip arthroplasty, venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary embolism (PE), which has gradually attracted people's attention in recent years due to its life-threatening potential.[1,2] It has been confirmed that DVT of the lower extremities is the main manifestation of VTE[3] and the death of patients due to PE also occurred after knee arthroscopic surgery[4,5] with a relatively low incidence.[6,7] At the present time, the use of anticoagulation in patients undergoing knee arthroscopic surgery remains controversial.[6,7] Previously, the American College of Chest Physicians (8th Edition) has pointed out that conventional anticoagulation is not required after arthroscopic surgery unless there exist other risk factors that may cause DVT.[8]

Recent studies have shown that the incidence of DVT after knee arthroscopy was 1.50%-41.20% without anticoagulation during the perioperative period.[6] Sun et al[7] found the total DVT incidence verified by venography after arthroscopic knee surgery was 14.90%, of which only 3.70% were symptomatic and asymptomatic DVT accounted for 11.20%. Subsequently, DVT is confirmed to be occurred in 21.90% of the patients after arthroscopic posterior cruciate ligament reconstruction with venography examination, among DVTs, 10.16% were asymptomatic and 11.72% were symptomatic.[9] Considering the

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objective factors such as the high-energy mechanism of posterior cruciate ligament (PCL) injury, relatively long operation time, and special anatomical structures of PCL, Dong et al stated that postoperative DVT incidence diagnosed by ultrasound following PCL reconstruction without thromboprophylaxis was 17.40% and a high proportion of asymptomatic thrombosis existed.[1] In a study of 30 patients with PCL rupture who underwent arthroscopic reconstruction, Hagino et al[10] evaluated DVT based on postoperative symptoms and found no symptomatic thrombosis. Notwithstanding this, clinical symptoms alone are not sufficient for making a definitive diagnosis of DVT. Together, the above findings potentially implicated the necessity of effective auxiliary examination and anticoagulant intervention for DVT in these patients.

Some epidemiological studies have shown that common risk factors such as age, gender, and body mass index (BMI) can partly affect the occurrence of DVT.[11] To our best knowledge, researches on whether perioperative prophylaxis should be used in patients undergoing knee arthroscopic PCL surgery and how to do a targeted anticoagulant therapy in these patients have yielded conflicting results.[1,9] Still, DVT prophylaxis may potentially lead to the risks of deep inflammation, bleeding events, and prolonged wound drainage.[12] Several lines of evidence suggest that the complication rate is highest for PCL reconstruction of all knee arthroscopic procedures.[13] For the first time, we herein aim to provide a comprehensive and systematic analysis on common risk factors of DVT after arthroscopic PCL reconstruction in patients with only PCL injury for a better guiding on the prevention and treatment of DVT in clinic.

Materials and Methods

Patients and Blood Sampling

From August 2014 to December 2020, a total of 172 patients who received knee arthroscopic PCL reconstruction due to PCL injury or rupture were consecutively enrolled in our department. All patients were diagnosed by clinical symptoms (such as limited knee mobility, etc.), physical examination, and MRI imaging. The color Doppler Ultrasound of both lower limbs was performed within 24 hours after admission and on the 3rd day after surgery. Exclusion criteria of the patients were: (1) congenital or secondary coagulation abnormalities (i.e., hemophilia A, B, C; Von Willebrand's disease; congenital coagulation factor I, II, V, VII deficiency; vitamin K1 deficiency, severe infection, liver diseases, etc.); (2) severe liver and kidney function intolerance to surgery; (3) a history of VTE and VTE events within half a year; (4) anticoagulant, lipid-lowering, or steroid drugs therapy within half a year; (5) a history of lower limb vein surgery; (6) the injury of PCL combined with other ligaments; (7) DVT before arthroscopic surgery.

The height and weight of all patients were measured by the same nurse after admission and the corresponding BMI values were then calculated and recorded. A range of normal BMI is from 20 to 25 kg/m^2, overweight is considered as a BMI of 25.1 to 29.9 kg/m^2, and obesity is defined as a BMI of 30 kg/m^2 or higher.[14] Accordingly, BMI values were divided into 2 categories: < 25 kg/m^2 and ≥ 25kg/m^2 in this study. Clinical data of each patient was collected according to their self-report, which mainly includes age, hypertension, diabetes, and smoking status.

Two tubes of 5 ml venous blood were obtained from every untreated patient by standard venipuncture at 7.00 a.m. after over-night fasting (12-14 hours) on the first day after admission, of which one tube of blood was centrifuged at 4°C and the serum sample was immediately sent to the clinical laboratory of our hospital. Serum levels of triglycerides (TG) and total cholesterol (TC) were then detected. Meanwhile, another tube of blood was used to detect the platelet count. On the 3rd day after surgery, 5 ml of blood of each post-surgery patient was also collected in the morning to measure the prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and the levels of fibrinogen (FIB) and D-dimer by full-automatic coagulation analyzer (Sysmex CA7000, Japan). Thereinto, PT, APTT, TT, and FIB were tested by solidification method and D-dimer was measured by immunoturbidimetry. The rising temperature and redness of the skin around the knee and calf, pain in the calf on dorsiflexion (Homan test), calf tenderness (Neuhof test) was conventionally examined and recorded by the same doctor following the surgery. This study was approved by the ethical committee of The Third Affiliated Hospital of Soochow University and Changshu Hospital Affiliated to Nanjing University of Chinese Medicine, and all patients signed the informed consents.

Surgery and DVT Prophylaxis

All the operations were performed under general anesthesia in the supine position by 3 senior surgeons. A thigh tourniquet inflated to 270 mmHg was used on the operated leg, which was deflated if the procedure lasted more than 90 minutes and was reinflated 10 minutes later if necessary. The use time of tourniquet in all patients was less than 90 minutes in this study. For patients undergoing arthroscopic PCL reconstruction, a single tunnel combined with autologous hamstring tendon reconstruction was used by the same surgeon. All patients were not given anticoagulant therapy before and after surgery, and only mechanical and physical prevention for DVT was performed. For every patient, the operated leg was bandaged with the moderate pressure and postoperative pneumatic compression was applied for 30 minutes twice per day with a lasting time of at least 10-14 days until discharge. Isotonic, progressively restrictive exercises for the quadriceps and ankle pump were begun 24 h after operation. All patients were equipped with knee joint adjustable braces for weightless flexion and extension training.

DVT Diagnosis and Therapy

Considering that the color Doppler ultrasound is a non-invasive test with low cost and high specificity for the diagnosis of acute

DVT,[1] all patients underwent ultrasound examination of bilateral lower extremity veins on postoperative day 3 by 1 experienced radiologist. The DVT diagnostic criteria are: (1) absence of venous flow; (2) complete non-compressibility of the vein; (3) the presence of an echogenic thrombus mass in the normally anechoic vein. According to the results of ultrasound, DVT involving in the iliac, femoral, or popliteal veins on either side of the limb was classified as a proximal DVT,[15] and the rest of the DVTs present in the calf veins were defined as distal DVTs. Patients with DVT on either leg were assigned to the DVT group. According to 2009 and 2016 editions of "Chinese Major Orthopedic Surgery of Venous Thrombosis Prevention Guidelines" and our own experience, the thrombolytic dose (subcutaneous dose of 0.4 ml or 100 IU/kg every 12 hours) of LMWH was applied to treat proximal thrombosis and thrombosis involving the fibular vein and posterior tibial vein for 7-10 days and continue to take rivaroxaban orally (10 mg per day) until 3 months following surgery. For the remaining distal DVTs, we routinely use LMWH with a conventional dose (0.4 ml per day) to do anticoagulant therapy for at least 1 week and continue oral rivaroxaban after discharge for at least 5 weeks. Ultrasound examination were done every 3 days to monitor the change of DVT and each DVT patient was re-examined no less than twice during hospitalization. Proximal DVT patients were discharged only when DVT improved such as partial dissolution of the thrombosis, etc. At the time point of 6 weeks and 3 months after surgery, the outcome of DVT was reassessed on ultrasonography.

Statistical Analysis

The comparison of categorical variables between 2 groups was performed using the $\chi 2$ test and the continuous variables were performed using the Student's test. The multivariate analysis was performed by Logistic regression analysis. In all the tests, a 2-tailed probability value of less than 0.05 was considered to be statistically. All the data were analyzed by SPSS 22.0 (SPSS, Chicago).

Results

DVT Incidence

There were 26 patients in the DVT group, including 18 males and 8 females, with an average age of 43.62 $\pm$ 13.28 years, and 146 patients in the non-DVT group, including 108 males and 38 females, with an average age of 33.96 $\pm$ 11.86 years. The incidence of DVT after knee arthroscopic PCL reconstruction was 15.12% (26/172) (Table 1). Additionally, DVT incidence was 14.29% (18/126) and 17.39% (8/46) among male and female patients, respectively (Table 2). Of all the 26 DVT patients, proximal DVT was detected in the popliteal vein in 4 patients (2.33%) (Table 2). Among the distal cases, 10 involved $\geq$2 veins. Notably, 16 of the 26 patients were asymptomatic (61.54%) and the rest 10 patients (38.46%) with symptomatic DVT showed limb swelling, pain, or high skin temperature. After the treatment of proximal and distal DVTs with a thrombolytic or conventional dose of LWMH, all DVTs appeared partial dissolution during the hospital stay except for one case of thrombosis involving the peroneal and muscular

Table 1. DVT Locations.

Locations	no.
Proximal DVT	4
Iliac vein	0
Femoral vein	0
Popliteal vein	4
Distal DVT	22
Anterior tibial vein	0
Posterior tibial vein	2
Peroneal vein	2
Muscular veins	8
Muscular + peroneal veins	6
Muscular + peroneal + anterior tibial veins	2
Muscular + peroneal + posterior tibial veins	2

Abbreviations: DVT, deep vein thrombosis; no, number.

Table 2. Clinical Characteristics of Patients.

Clinical characteristics	DVT patients	Non-DVT patients	*P* value
Patients, no.	26	146	-
Gender (male/female, no.)	18/8	108/38	$P = 0.615$[a]
Mean age, years (SD)	43.62 (13.28)	33.96 (11.86)	$P \leq 0.001$
Mean BMI, kg/m^2 (SD)	26.20 (2.94)	23.73 (3.96)	$P = 0.003$
(< 25 kg/m^2, no.)	6	100	-
($\geq$ 25 kg/m^2, no.)	20	46	$P \leq 0.001$[a]
Diabetes mellitus, (with/without, no.)	2/24	4/142	$P = 0.257$[b]
Hypertension, (with/without, no.)	4/22	12/134	$P = 0.428$[c]
Smoking, (with/without, no.)	8/18	34/112	$P = 0.413$[a]
Homans test (+/−, no.)	10/16	12/134	$P \leq 0.001$[c]
Neuhof test (+/−, no.)	10/16	8/138	$P \leq 0.001$[c]
TG, mmol/L (SD)	1.34 (0.47)	1.52 (1.27)	$P = 0.478$
TC, mmol/L (SD)	4.49 (0.66)	4.39 (0.82)	$P = 0.722$
Platelet count, 10^{12}/L (SD)	219.92 (55.75)	208.70 (60.97)	$P = 0.383$
Duration of surgery, min (SD)	105.39 (20.64)	99.00 (21.48)	$P = 0.162$
Duration of tourniquet, min (SD)	73.39 (13.40)	69.11 (14.70)	$P = 0.168$
PT, s (SD)	11.76 (0.87)	11.56 (0.66)	$P = 0.164$
APTT, s (SD)	28.62 (3.67)	28.06 (4.20)	$P = 0.524$
TT, s (SD)	15.76 (1.41)	16.02 (1.65)	$P = 0.456$
FIB, g/L (SD)	4.17 (0.95)	4.40 (4.35)	$P = 0.796$
D-dimer, mg/L (SD)	1.81 (1.95)	0.62 (0.52)	$P \leq 0.001$

Abbreviations: DVT, deep venous thrombosis; no, number; SD, standard deviation; BMI, body mass index; TG, triglycerides; TC, total cholesterol; min, minute; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; FIB, fibrinogen.
[a]Pearson Chi-square test.
[b]Likelihood ratio χ^2 test.
[c]Continuous correction test.

Table 3. Risk Factors of Postoperative DVT.

Risk factors	OR	95% CI	*P* value
Gender	1.051	0.221-5.002	$P = 0.951$
Age	1.090	1.025-1.158	$P = 0.006$
BMI	1.509	1.181-1.929	$P = 0.001$
Diabetes mellitus	0.617	0.025-15.118	$P = 0.767$
Hypertension	0.951	0.045-20.099	$P = 0.974$
Smoking	1.033	0.153-6.965	$P = 0.973$
TG	3.104	1.019-2.566	$P = 0.009$
TC	1.950	0.637-5.971	$P = 0.242$
Platelet count	0.998	0.984-1.012	$P = 0.732$
Duration of surgery	1.004	0.967-1.044	$P = 0.819$
Duration of tourniquet	1.031	0.964-1.103	$P = 0.373$
PT	1.017	1.497-1.818	$P = 0.109$
APTT	0.865	0.676-1.107	$P = 0.251$
TT	1.131	0.718-1.782	$P = 0.594$
FIB	0.677	0.320-1.434	$P = 0.309$
D-dimer	5.034	2.091-12.117	$P \leq 0.001$

Abbreviations: BMI, body mass index; TG, triglycerides; TC, total cholesterol; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; FIB, fibrinogen.

veins without significant changes, which was mainly manifested by the reduction of thrombosis diameter or size on ultrasound images. At 6 weeks and 3 months postoperatively, 4 popliteal DVTs and 22 distal DVTs were found thoroughly dissolved and blood vessels recanalization were obtained. There were no anticoagulation and thrombolysis complications and symptoms of PE in all patients at follow-up.

General Comparison

In Table 2, there was no statistical difference in the distribution of patients' gender ($P = 0.615$) between DVT and non-DVT patients. It is worth noting that DVT group has the significantly higher BMI ($P = 0.003$), age ($P \leq 0.001$), and postoperative D-dimer levels ($P \leq 0.001$) than non-DVT group. Also, there existed more overweight and obese patients ($P \leq 0.001$) and higher positive rates of Homan test ($P \leq 0.001$) and Neuhof test ($P \leq 0.001$) in DVT patients than those in controls. However, there were no significant differences in blood TG, TC, and FIB levels, platelet count, operation time, and tourniquet using time ($P > 0.05$). A parallel distribution of diabetes, hypertension, and smoking was observed between 2 groups ($P > 0.05$).

Multivariate Analysis

In the multivariate analysis (Table 3), an older age (OR = 1.090; 95% CI = 1.025-1.158; $P = 0.006$), a high BMI (OR = 1.509; 95% CI = 1.181-1.929; $P = 0.001$) and an increased post-surgery D-dimer (OR = 5.034; 95% CI = 2.091-12,117; $P \leq 0.001$) value were significantly associated with an elevated DVT risk after knee arthroscopic PCL reconstruction. In addition, we failed to find any significant association of DVT incidence and other risk factors in this study ($P > 0.05$).

ROC Analysis

In the ROC analysis, we calculated the area under curve (AUC) of different risk factors and found age, BMI and D-dimer were predictive factor of postoperative DVT. The ROC curves of the 4 risk factors were shown in Figure 1. The AUC of age, BMI and D-dimer were 0.713, 0.709, and 0.864, respectively (Table 4).

Discussion

In this study, we retrospectively investigated the common risk factors for DVT after knee arthroscopic PCL reconstruction in patients with only PCL injury and excluded the potential impacts of multiple ligaments injury. Obviously, the older age is a risk factor for DVT after PCL reconstruction. By the multivariate analysis, an elevated BMI value (BMI ≥ 25 kg/m^2) was associated with a 0.51-fold increased risk of DVT postoperatively. Also, postoperative DVT risk in patients with an increased D-dimer level was also 4.03 times higher than that in controls. It further indicated that these 3 elements might have underlying effects on post-surgery DVT.

In recent years, obesity has been proven to be an independent risk factor for VTE,[16] which is often accompanied by disturbances of lipid metabolism such as increased TG or reduced high-density lipoprotein cholesterol levels.[17] The existed findings suggested that some biological indicators related to lipid could exert a prothrombotic effect on thrombosis through multiple mechanisms.[18-20] It is plausible that the high BMI may eventually play a partial role in the development of VTE by affecting lipid metabolism which could acted on the coagulation and fibrinolytic system. As a kind of commonly used lipid-lowering drugs, statins have been confirmed to reduce the risk of VTE potentially.[21-23] Importantly, Delluc et al indicated that the anti-VTE effect of statins is likely due to its direct actions on the systemic coagulation mechanism.[21]

Previously, it has been suggested that the increase in subcutaneous fat and visceral fat caused by obesity can promote the secretion of multiple inflammatory cytokines such as C-reactive protein, tumor necrosis factor-α, interleukin-6, and interleukin-18.[24] Further, obesity has been thought to be a systemic and low-grade inflammatory disorder which is triggered by inflammatory cytokines secreted by adipocytes.[25] Two cohort studies emphasized that the relevance of BMI and VTE is partially initiated by CRP in both obese males and females.[26,27] Also, statins might reduce the occurrence of VTE by down-regulating the expression of inflammatory mediators.[23] Summarily, these existing research results ulteriorly illustrated that the low-grade inflammatory and impaired fibrinolysis state mediated by obesity itself was very likely to be a major reason for the increased risk of VTE.[25,28,29] Importantly, recent researches demonstrated that the abnormal expression of adipokines and microRNAs and the endothelial damage resulting from systemic oxidative stress could contribute to the pro inflammatory and prothrombotic effects exacerbated by excess body weight.[25,28,29] Although the specific association of a high

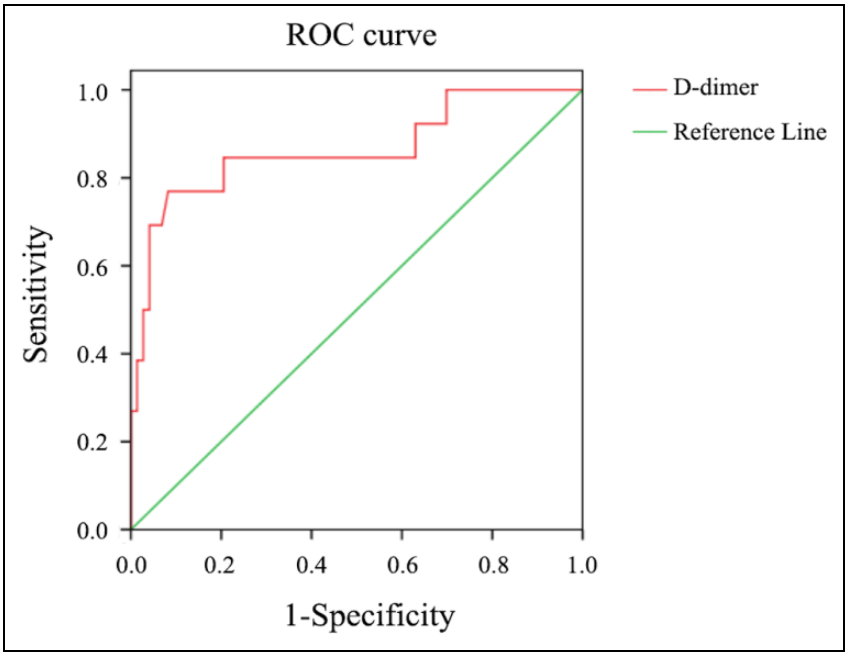

Figure 1. Receiver operating characteristic (ROC) analysis of D-dimer to predict postoperative DVT.

Table 4. The ROC Results of Risk Factors to Predict Postoperative DVT.

Risk factors	Sensitivity (%)	Specificity (%)	AUC	95% CI	SE	*P* value
Age	84.6	52.1	0.713	0.600-0.826	0.058	0.001
BMI	69.2	74.0	0.709	0.612-0.805	0.049	0.001
D-dimer	76.9	90.4	0.864	0.772-0.955	0.047	<0.001

BMI and VTE is still not clear, for the obese patients with PCL injury, there is quite a necessity to take some measures exactly as strengthening physical prevention, taking lipid-lowering medication, and anticoagulant intervention for a decrease in DVT incidence after knee arthroscopic PCL reconstruction.

For all we know, age has been identified as a VTE risk factor mainly due to the increased blood coagulability and prevalence of other predisposing factors such as immobilization and hospitalization.[28,30,31] In this study, an older age was weakly associated with a higher DVT risk, which suggested that age was still an unignorable factor in DVT prevention. D-dimer is widely used in clinical practice as an indicator to monitor DVT with a high sensitivity and specificity.[32] Although the D-dimer level is affected by inflammation, bleeding, and some other factors,[9] effective anticoagulation is still necessary for patients with high D-dimer levels after knee arthroscopic PCL reconstruction. Considering the fact that the hypercoagulable status of patients after surgery usually lasts no more than 48 hours which is the peak period of the formation of acute DVT in the lower limbs,[7] the blood D-dimer level was routinely measured on postoperative day 3 in this study and then the ultrasound of both legs was performed. This might largely ensure the reliability and accuracy of our findings. Follow-up studies will continue to be focused on the monitoring of D-dimer levels in such patients in order to better predict and assess the initiation, progress and outcome of postoperative DVT.

The incidence rates of symptomatic and asymptomatic DVT were 5.81% (5/86) and 9.30% (8/86) respectively, which were also close to the findings of Sun et al.[7] Furthermore, it was worth mention that the positive rate of Homans and Neuhof tests in DVT group was significantly higher than that in non-DVT group, which largely implied that DVT after knee arthroscopic PCL reconstruction was usually associated with some corresponding symptoms and signs. Therefore, timely and targeted anticoagulation for patients with symptoms postoperatively may reduce the risk of DVT to a certain extent. Although the long-term risk of symptomatic or asymptomatic DVT after knee arthroscopy is still unknown and allow for the relatively high incidence of asymptomatic DVT (9.30%) in this study, it is still necessary to make a clear diagnosis of DVT by using ultrasound and further perform an effective intervention. Definitely, find more specific and predictable risk factors associated with postoperative DVT is also an issue that needs to be solved.

In this study, the Doppler ultrasound of both lower limbs were used as the criteria for diagnosing DVT and the common risk factors of DVT after knee arthroscopic PCL reconstruction in patients with only PCL injury were systematically analyzed.

However, a limitation is that we only examined DVT incidence in normal, relatively young patients and provided no information on some other clinical characteristics including cancer, hormone use, physical activity, menopausal status, etc. Due to the limited sample size and the relatively high cost of blood tests, we were not able to do an in-depth analysis after stratified by gender and taken into account more potential biomarkers such as blood viscosity and coagulation factors. In addition, we failed to conduct a dynamic monitoring on DVT including preoperative thrombosis and D-dimer values. The specific change law of D-dimer during the perioperative period may be of considerable importance. After DVT was found, there was still a lack of correlation analysis for the location, size, and resolving of DVTs after surgery. In spite of this, the conclusions of our study may contribute to the comprehensive control of DVT in these patients.

Conclusion

In conclusion, a high BMI and an elevated postoperative D-dimer level are risk factors for DVT after knee arthroscopic PCL reconstruction in patients with PCL injury. DVT prophylaxis and prevention in these patients is still of certain importance. To better assess the efficacy and safety of thromboprophylaxis in patients after arthroscopic PCL reconstruction, a randomized clinical trial would be required.

Authors' Note

Pu Ying and Xiaoyu Dai designed the study and wrote the article. Xiaowei Jiang, Yue Xu and Lei Zhu collected the clinical data and made the postoperative DVT diagnosis. Wenge Ding, Yi Xue and Qiang Wang did the operations. Pu Ying and Xiaoyu Dai did the data analysis and revised the manuscript. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

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