REVIEW ARTICLE

Characteristics of Deep Venous Thrombosis in Isolated Lower Extremity Fractures and Unsolved Problems in Guidelines: A Review of Recent Literature

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Abstract

Deep venous thrombosis (DVT) has been characterized by a disorder of venous return caused by abnormal blood clotting in deep veins. It often occurs in the lower limbs and is a common complication in orthopaedics. Therefore, relevant professional organizations domestic and overseas had formulated and constantly updated relevant guidelines to prevent the occurrence of DVT. According to the management strategy of the guidelines, the incidence of DVT can be significantly reduced. However, due to the variety of fractures types, the guidelines cannot expound precautions and characteristics of DVT for all fracture types at present, and there are other related unresolved problems. For example, there is still a lack of consistent optimal strategies for the management of DVT following isolated lower extremity fractures with a higher incidence. The best anticoagulant strategies for patients with upper limb fractures, pediatric fractures, and those combined with other injuries are rarely described in orthopaedic guidelines, but such fractures are common in clinical orthopaedics. The long-term complications after DVT, such as post-thrombotic syndrome, are not well-understood. In the absence of clear guidance, orthopaedic surgeons often resort to empiric anticoagulation or conservative treatment, so the prevention effects of DVT are inconsistent. The purpose of this review is to summarize the characteristics of DVT events after isolated lower extremity fractures and to discuss the unsolved issues in the guidelines by reviewing the previous literature and tracing the history of DVT discovery, to provide more scientific and comprehensive recommendations for the prediction and prevention of DVT.

Key words: deep venous thrombosis; epidemiology; forecasting; isolated lower extremity fractures; prevention

Introduction

At present, the latest guidelines or expert consensus on prevention and screening of perioperative venous thrombosis in orthopaedic patients published in China including the 2016 Edition of Guidelines for the Prevention of Venous Thromboembolism in Orthopedic Major Surgery in China, The 2013 Edition of Expert Consensus on Screening and Treatment of Deep Venous Thrombosis on Orthopedic Trauma Patients, and the 2012 Edition of Guidelines for the Prevention of Perioperative Venous Thromboembolism in Orthopedic Trauma Patients. The United States and Europe had also published relatively new guidelines. Although the time and organizations of these guidelines are different, they are all based on evidence-based medicine and related literature. It has been confirmed that only strictly following the guidelines can significantly reduce the incidence

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of deep venous thrombosis in clinical practice. However, there are also contradictions among the guidelines. For example, the relevant guidelines in China point out that patients with isolated single fractures far from the knee joint who intend to undergo surgery do not need drug thromboprophylaxis unless there are related risk factors. The United Kingdom guidelines recommend anticoagulant therapy, while the American College of Chest Physicians (ACCP) does not mention such content. However, in practice, such injuries are very common in clinical work. Whether anticoagulant therapy is needed after upper limb fracture is rarely mentioned or not stated in the relevant guidelines. However, recent literature had pointed out that the incidence of deep venous thrombosis (DVT) after this type of fracture is higher than previously thought. Therefore, it is necessary to search relevant literature to discuss this situation. Due to the deepening of understanding of DVT, the complexity of the initial injury, and the lack of evidence-based evidence, there are still some unsolved problems, such as: (i) What is the incidence and distribution characteristics of preoperative deep vein thrombosis in clinically common isolated lower extremity fractures such as femoral shaft fractures, distal femoral fractures, patella fractures, tibial plateau fractures, tibiofibular shaft fractures, and ankle fractures? (ii) What are the more easily available predictors of DVT before surgery? (iii) Do these patients need anticoagulant therapy if they need non-surgical treatment or long-term immobilization due to other factors before the operation? (iv) Can postthrombotic syndrome (PTS) be used as an indication to prevent DVT? (v) What is the outcome of treatment for deep vein thrombosis? (vi) Is the incidence of deep vein thrombosis after upper extremity fractures as low as previously recognized, and is there no need for preventive DVT therapy? (vii) What are the risk factors of DVT in children following fractures? What is the incidence? Is routine prevention needed? If necessary, is it the same as for adults? (viii) For patients with anticoagulation contraindications to drugs, which type of inferior vena cava filter is better, and what are the complications? (ix) For patients with other injuries such as craniocerebral trauma or thoracoabdominal injuries, if anticoagulation is needed, when is the safe time to start drug treatment?

Based on the above-unsolved problems, this review summarizes the solution of the above problems in detail by consulting the latest relevant literature to guide orthopaedic surgeons to make more scientific clinical decisions.

Methods

First, we searched PubMed, Web of Science, China National Knowledge Infrastructure, and Wanfang databases for related studies without language restrictions from March 2011 to March 2021. The following main search terms were used: ("femoral shaft fractures" [Title] OR "distal femoral fractures" [Title] OR "patella fractures" [Title] OR "tibial plateau fractures" [Title] OR "tibiofibular shaft fractures" [Title] OR "ankle fractures" [Title] OR "upper extremity fractures" [Title] OR "Pediatric Trauma" [Title]) AND ("deep venous thrombosis" [Title] OR "epidemiology" [Title] OR "risk factors" [Title]). Then we also searched the same databases above with terms as follows: "post-thrombotic syndrome" [Title] OR "inferior vena cava filter" [Title]. The relevant important references were also included. A total of 937 relevant articles were retrieved, excluding duplicate articles, abstracts, letters, and articles unrelated to the theme. In addition to the relevant important references searched manually, 101 pieces of literature were included at last. The flow chart of literature searching and screening is shown in Figure 1.

The Origin and History of Deep Venous Thrombosis

The first description of lower extremity DVT appeared in the Middle Ages[1,2]. Guillaume de Saint pathus, a French Franciscan monk, described in his manuscript "La Vie et les miracles de Saint Louis" as follows: in 1271, Raoul, a 20-year-old shoemaker, suffered from pain and swelling in his right leg, which then extended to his thigh. Subsequently, the patient's condition worsened, with leg ulcers and bone exposure. Limited by medical knowledge and religious authority at that time, the patient paid homage to the tomb of King St. Louis and sprinkled the dust around the tomb on the ulcer surface of the affected limb. Unexpectedly, the disease was miraculously cured. In 1676, Richard Wiseman, a British surgeon, described the swelling and pain of a pharmacist's wife's right knee to hip caused by fatigue. He proposed for the first time that the cause of thrombosis might be the change of circulating blood itself and that thrombosis could extend from the distal end of the limb to the proximal end[3]. Theoretically, pregnancy and the postpartum period

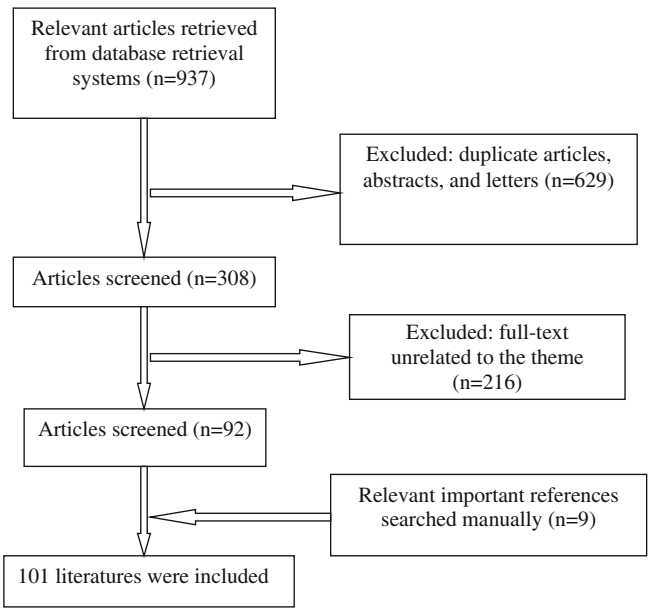

Fig. 1 The flow chart of relevant literature retrieval from databases

are the high-risk stages of lower extremity venous thrombosis. However, until the end of the 18th century, it was thought that the disease was caused by the "evil liquid" in the lower extremity or the milk not consumed in the leg. In 1793, British anatomist John Hunter denied the prevalent body fluid theory and believed that a thrombus was a clot in the blood blocking the vein. In the middle of the 19th century, Jean cruveilhier, a French professor of pathology, put forward the famous theory of phlebitis[4]. In 1846[5,6], when studying the theory of phlebitis, Rudolph Virchow discovered two types of blood clots: primary blood clot and drift-diffusion blood clot. The latter perfectly explained the question that had puzzled the medical community for a long time, that is, where did the pulmonary blood clot come from in patients with the sudden death of pulmonary embolism? Later, through the observation and study of a large number of cases of postpartum thrombosis, the famous three elements theory of venous thrombosis was put forward: venous injury, slow blood flow, and hypercoagulable state in the blood.

In 1866, Armand Trousseau[7,8] found that patients with visceral malignant tumors often had painful swelling of limbs through autopsy and first described the relationship between venous thrombosis and tumor. In 1955[9] the study of 748 patients showed that pelvic and lower extremity fractures surgery was the second risk factor of venous thrombosis. With in-depth understanding, a large number of risk factors related to DVT including genetic factors had been found. By tracing the cognitive process of DVT, we can not only remember the medical sages but also perceive their acute observation and innovative research spirit to inspire medical successors. Just as Percival Pott said, a famous British surgeon in the 18th century, "My lamp is almost extinguished, I hope it has burned for the benefit of others"[10].

The Incidence and Distribution of DVT in Patients with Isolated Lower Extremity Fractures before Operation

At present, there is a consensus on the prevention of venous thrombosis in hip fractures and hip or knee arthroplasty in the guidelines of various countries. However, there are few studies on the other common fractures of the lower extremity, such as femoral shaft fractures, distal femoral fractures, patellar fractures, tibial plateau fractures, tibiofibular shaft fractures, and ankle fractures. In this review, the incidence and distribution characteristics of deep vein thrombosis in the above fractures are described.

Femoral Shaft Fracture

As early as 1961, Sevitt and Gallagher[11] found that DVT occurred in six of seven patients with femoral shaft fracture who did not receive thrombosis prevention. In 1996, Abelseth *et al.*[12] found that the incidence of occult DVT was 28% in 102 patients with distal hip fractures, of which eight cases (40%) of DVT occurred in 20 cases of femoral shaft fractures and found that the closer to the proximal limb fractures, the higher the incidence of DVT. Wang *et al.*[13] studied the incidence of preoperative DVT in 1825 patients with isolated lower extremity fractures. The DVT occurred in the popliteal vein and its proximal end was defined as proximal DVT, while the thrombosis that occurred far away from the popliteal vein was defined as distal DVT. If there were thrombosis in the popliteal vein both proximal and distal end, it was classified as proximal DVT. On average 3.5 days after injury, 64 of 159 patients with femoral shaft fractures developed DVT (40.3%), including 19 proximal DVT (11.9%) and 45 distal DVT (28.3%). Most of the DVT occurred on the fractured leg. The incidence of DVT on the uninjured legs was only 1.6%, and 3.3% on both sides. However, another cadaveric study[11] showed that the incidence of DVT on the fractured side was the same as the uninjured. The difference between the two results may be due to different subjects. Qu *et al.*[14] found that the incidence of preoperative DVT for femoral fracture was 77.9%, most were peripheral DVT (93.6%, including popliteal vein). Li *et al.*[15] found that 17 of 139 cases of femoral shaft fractures had DVT before the operation, the incidence rate was 12.2%, but he did not indicate the specific location of the thrombosis. Li *et al.*[16] found that in 35 cases of femoral shaft fractures, DVT occurred in 10 cases (28.6%) within 24 h before the operation, including seven cases of distal DVT, one case of proximal DVT, and two cases of mixed thrombosis. Another study by Zhang et al.[17] found that nine of 32 femoral shaft fractures had DVT (28.1%) before the operation, and the incidence was the highest in all lower limb fractures. Guo *et al.*[18] screened 39 cases of femoral shaft fracture with multi-slice spiral CT venography (MSCTV) before operation and found that 13 cases (33.3%) had DVT, most of which were peripheral thrombosis. Lv *et al.*[19] found that DVT occurred in 26 of 133 cases of femoral shaft fracture (19.5%), which was higher than intertrochanteric fractures. According to an epidemiological survey[20] in a large sample of fracture patients (24,049 cases, excluding hand and spine fractures), the incidence of DVT in femoral shaft fractures was 14.7% (178/1209), which was higher than 12.9% in hip fractures, 7.31% in pelvis and acetabulum fractures. Zhu *et al.*[21] conducted a study of DVT in 600 cases of fracture showing that the incidence was 23.6% (34/144). Another study[22] involving femoral shaft fractures showed that the incidence of DVT was 26.9% (18/67). Another study[23] also obtained similar results, the incidence of DVT after femoral shaft fracture (20.7%) was higher than hip fracture (20.3%). Wang *et al.*[24] studied the incidence of DVT in 78 cases of young and middle-aged femoral shaft fractures and found that 17 cases (21.8%) had DVT. Sun *et al.*[25] studied 237 cases of femoral shaft fractures and found that 54 cases (22.78%) had DVT during the perioperative period. Sun *et al.*[26] studied the effect of anticoagulation and non-anticoagulation on DVT in 208 patients with femoral shaft fracture. It was found that the incidence of DVT in the anticoagulation group was 7.8% (9/115) within 1 week before the operation, while the incidence in the non-anticoagulation group was 12.9% (12/93).

Sun *et al.*[27] analyzed 147 patients with DVT of the lower extremity and found that the femoral shaft fracture accounted for 18% (10/56) in the proximal thrombosis group. Logistic regression analysis showed that femoral shaft fracture was significantly associated with proximal thrombosis.

The incidence of preoperative DVT in the femoral shaft was more reported in the previous relevant literature, and the data were consistent. Most researchers believed that the probability of preoperative DVT was higher, even higher than that of hip fracture, and the distal DVT was more than the proximal DVT, the fracture site was far more than the uninjured.

Fracture around Knee Joint

There are three types of fractures around the knee: distal femoral fractures, tibial plateau fractures, and patellar fractures. Up to now, the incidence of DVT in the fractures above was reported in as whole or individually in the literature. The summary is as follows.

Zhang *et al.*[28] reported the incidence of preoperative DVT in 160 patients with distal femoral fractures over 65 years old. The incidence rate was 52.5% (84/160), of which the proximal DVT accounted for only 1.3%, the mixed type was 25.0%, and the distal was 26.3%. About 12 days after anticoagulant therapy, 45.2% of the DVT had complete recanalization. Another study[15] showed that the incidence was 9%, the incidence rate was different from that of Zhang *et al.*[28]; this may be due to the age differences between the patients in the two studies. Li *et al.*[16] found that the incidence of DVT was 24.8% but mainly distal type. Another domestic study[17] reported the rate was 35.5%. Guo *et al.*[18] found that the total incidence of DVT around the knee was 38.6% (17/44). The incidence of DVT was 26.1% in thromboprophylaxis patients while 43.9% without thromboprophylaxis. Lv *et al.*[19] showed that the incidence of DVT around the knee was 11.6%, including 21.9% (21/96) of femoral intercondylar supracondylar fractures and 19.0% (19/248) of tibial plateau fractures. Zang *et al.*[20] found that the highest incidence of DVT was supracondylar and intercondylar fractures of the femur, which were 23.04% (165/716), even higher than 14.72% (178/1209) of femoral shaft fractures. Dong *et al.*[23] reported the incidence of DVT was 14.5% (11/75) around the knee fracture. According to a study in Japan[29], the incidence rate of fractures in patients with knee fractures without drug prophylaxis was up to 42.4% (14/33).

Tibial plateau fractures account for 32% of the knee fractures, and 17.3% to 23.9% of the patients would develop into DVT before operation[30]. Liu *et al.*[31] observed 192 of 1179 (16.3%) patients with tibial plateau fractures developed into preoperative DVT, which occurred on average (3.9 ± 3.6) days after injury. Another study[13] showed that the incidence of proximal and distal DVT was 3.4% and 20.5%, respectively, and the total DVT was 23.9% in 176 tibial plateau fractures. The incidence of DVT was higher in tibial plateau fracture without prophylaxis, up to 43%[12]. Fei *et al.*[32,33] and another study found that the incidence of preoperative DVT in tibial plateau fractures was reaching 43.9% or 60.4%. Li *et al.*[34] reported that the incidence of DVT in tibial plateau fractures was 36.43%.

Xiao *et al.*[35] compared the preoperative incidence of DVT in the tibial plateau fractures (50 cases) and the patella fractures group (50 cases) and found that the incidence in the tibial plateau fractures was 52%, while the incidence was 30% in the patella fractures. The thrombosis was mostly located in the popliteal vein, anterior tibial vein, and posterior tibial vein. Another study[13] showed the total incidence of DVT was 15.3% (9/59), 1.7% in the proximal vein, and 13.6% in the distal. A study[36] based on preoperative ultrasound examination of 114 patients with patellar fracture showed that 25 cases (21.9%) had DVT, including 24 cases (96.0%) of distal DVT and one case of proximal DVT. The changes of thrombus before and after operation were as follows: 23 cases of new thrombus, nine cases of thrombus disappeared. The new DVT included 21 distal thrombi, one proximal thrombus, and one case of mixed thrombus. The disappeared thrombus was all distal thrombus. Zang *et al.*[20] showed that the incidence of DVT in patella fractures (7.3%) was higher than that in the ankle (3.0%) and proximal tibia (5.8%).

Fracture of Tibia and Fibula

Gao *et al.*[37] found that 51 of 178 (28.65%) cases with tibiofibular fracture developed into DVT, including 14 cases of popliteal vein thrombosis, accounting for 13.7% (14/102). Another study[38] with a similar number of cases showed that 39 (21.7%) patients had preoperative DVT, 38 cases were distal thrombosis, and one case was mixed thrombosis. Other studies[16–18] reported that the incidence was lower, about 2.86% to 11.5%.

Ankle Fracture

Ankle fracture or sprain is the most common injury of the lower extremity, accounting for 19.2% and 39.3%, respectively. However, the incidence of DVT is low. A study[39] based on the national trauma database of the United States showed that the incidence of DVT and pulmonary embolism in 224,747 patients with foot and ankle injuries from 2010 to 2016 was 0.28% and 0.21%, respectively. Two meta-analysis studies[40,41] also showed that the incidence of DVT/PE in ankle surgery was less than 1%. However, Wang *et al.*[13] found that preoperative DVT of ankle fractures was 2.0% proximal DVT, and that of the distal end was 14.6%. Luo *et al.*[42] investigated 1532 patients with ankle fractures in a level one trauma center in China and found that the incidence of DVT was 6.4% (98/1532), of which the proximal DVT accounted for 16.5% and the distal DVT accounted for 83.5%. Duan *et al.*[43] retrospectively analyzed the incidence of preoperative DVT in 344 patients with foot and ankle fractures and found the total incidence was 13.66%, most of them were distal DVT (44 cases), and only three cases were

proximal DVT. Among them, the highest incidence of DVT was 25.64% (10/39) and occurred in Pilon fractures, followed by calcaneal (13.01%) and ankle fractures (11.05%). According to the data of 88,241 patients with foot and ankle fractures based on the British National Medical Center[44], the DVT and PE rates were 0.12% and 0.17%, respectively; the authors of the study also believe that VTE events were extremely rare, and no evidence supported that thrombosis prevention was beneficial. Therefore, it is considered that this kind of fracture did not need thrombosis prevention. The incidence of DVT and PE in 7896 patients or 14,777 patients with ankle fractures were both less than 1.0%, and most of the DVT was isolated asymptomatic distal thrombosis[45,46]. Therefore, many researchers believed that it might not be necessary to take precautions against DVT for ankle fractures.

Predictors are Easy to Measure before Surgery

Most of the previous studies used D-dimer or lower extremity venous ultrasound to evaluate or diagnose DVT in patients with fractures, but the former has poor specificity, and many factors can produce positive results, so D-dimer positive has little value in the diagnosis of DVT; at the same time, the latter has poor popularity and timeliness due to the limited indications, and depends on the professional level of the examiners, so the result may be inconsistent between different examiners or hospitals. Therefore, it is particularly important to find both cheap and reliable preoperative examination indicators that can be quickly obtained. Although guidelines had not included these details, it remains a hot topic in current research. With the deepening of study and more evidence-based medicine, the following indicators may become important to predicting DVT. It is summarized as follows.

Ma *et al.*[47] analyzed the predictive factors of DVT in 410 pre-operation patients with simply closed foot fractures and found that blood indexes related to the DVT, such as platelet distribution width (PDW) < 12%, high-density lipoprotein cholesterol (HDL-C) < 1.1 mmol/L, alkaline phosphatase (ALP) > 100 U/L, serum sodium concentration (Na^+) < 135 mmol/L. Another study[48] on simple tibial shaft fractures showed that the serum hydroxybutyrate dehydrogenase (HBDH) > 182 U/L was closely related to the occurrence of DVT. The reason may be that this index reflects the injury of red blood cells and muscles. The higher the value, the more severe the damage. Tibial shaft fracture is usually accompanied by soft tissue injury, which can activate the three factors of DVT formation, thus promoting the formation of DVT. Zhang *et al.*[28] studied the risk factors of preoperative DVT with distal femoral fractures. Multivariate analysis showed that C-reactive protein (CRP) > 11 mg/L and platelet (PLT) > 217 × 10^9/L were independent risk factors. Liu *et al.*[31] analyzed the blood indexes of 192 patients with tibial plateau fractures who developed into preoperative DVT and found that neutrophils > 5.02 × 10^9/L and PLT > 278 × 10^9/L were related to the occurrence of preoperative DVT. Luo *et al.*[42] studied 98 patients with preoperative DVT who suffered ankle fractures and found that ALB < 35 g/L and lymphocyte < 1.8 × 10^9/L were associated with DVT. Tan *et al.*[49] analyzed 716 patients with patellar fractures and found that low-density lipoprotein cholesterol (LDL-C) > 3.37 mmol/L was associated with DVT. Wu and Cheng[50] observed 569 patients with femoral and pelvic fractures and found that anemia, hypoproteinemia, and increased levels of fibrinogen degradation products were independent risk factors of preoperative DVT. Another study[49] on the risk factors of preoperative DVT of patellar fracture suggested that preoperative D-dimer > (4.5 ± 5.4) mg/L was related to DVT. Qu *et al.*[51] concentrated on knee fractures also confirmed a similar conclusion, the average value of D-dimer was (4.61 ± 3.34) mg/L. Similarly, Duan *et al.*[43] found that D-dimer > 300 ng/ml was an independent risk factor in foot and ankle fractures (including Pilon fractures, ankle, and calcaneal fractures), which increased the risk of thrombosis about three times before operation. Temraz *et al.*[52] analyzed the influence of perioperative blood sodium level on DVT in nearly 100,000 fractures and believed that hyponatremia or hypernatremia increased the risk of DVT (1.43 times and 1.56 times, respectively). Zander *et al.*[53] concentrated on the relationship between preoperative blood transfusion and DVT in trauma patients and found that the increase of fresh frozen plasma (FFP) transfusion was associated with the increased risk of DVT in patients with less than 4U blood transfusion, and each unit of FFP increased the risk by 25%. However, FFP did not increase the risk when the blood transfusion exceeds 4U.

Anticoagulant Therapy on Conservatively Treated or Long-Term Immobilized Patients Remains Controversial

The consensus of Chinese experts pointed out that for patients with femoral fractures, fractures around the knee, and multiple fractures far away from the knee, it was recommended that drugs should be used to prevent DVT before the operation, while for single fractures far away from the knee, anticoagulation was not required if there were no related risk factors[54]. However, if the fractures above were treated conservatively, such as using a brace or cast to fix the affected limb for a long time, it was not clear whether anticoagulation was needed. In the latest version of VTE guidelines, the American College of Chest Physicians (ACCP) did not mention the need for preventive medication[55]. While the American College of Foot and Ankle Surgeons (ACFAS) considered that fixation due to ankle fractures for more than 4 weeks was a major risk factor for DVT, so they recommended drug prophylaxis[56].

Testroote *et al.*[57] undertook another study which included 1490 patients who had been immobilized in the lower extremity for at least 1 week, compared the incidence of DVT in the low molecular heparin anticoagulation group and the non-anticoagulant group. Ultimately, the incidence of the anticoagulant group was significantly lower than that

of the control group, so he suggested that anticoagulant drugs should be used. Bruntink *et al.*[58] compared the incidence between anticoagulant and non- anticoagulant in 270 patients with foot and ankle fractures who fixed with a cast for at least 4 weeks and found that the incidence of DVT in the former was 1%∼2% and 12% in the latter. Anticoagulant drugs did not cause obvious bleeding and other complications. They also suggested anticoagulant treatment for such patients. Jørgensen *et al.*[59] used venography to evaluate the incidence of DVT, 300 patients fixed with a cast for at least 3 weeks were included. They found that the incidence of DVT was 18% in young patients without anticoagulant treatment and one 33-year-old patient developed massive clots that blocked the iliac vein, so anticoagulation was also recommended. Nesheiwat and Sergi[60] reported a 28-year-old male patient with Achilles tendon injury caused by playing basketball, and then the patient underwent knee cast fixation without prophylactic anticoagulation. Seven days after injury, he was hospitalized again due to dyspnea and chest pain and was diagnosed with pulmonary embolism and popliteal vein thrombosis of the affected extremity. Later, the author reviewed about 100 cases of lower extremity fractures with plaster fixation in his hospital and discovered four patients developed into DVT (three ankle fractures and one Achilles tendon rupture), with an incidence of 4%. It was worth noting that none of these patients with DVT had the risk factors indicated in the previous guidelines. Therefore, anticoagulant therapy was recommended for patients with immobilization for more than 4 weeks. Kock *et al.*[61] compared the effects of low molecular weight heparin on DVT in patients with lower limb fractures fixed with a cast under or above the knee. The results showed that seven of 163 (4.3%) patients with a placebo developed into DVT, while no DVT occurred in the low molecular weight heparin group. Anticoagulant therapy was also recommended for such patients. Lapidus *et al.*[62] studied the anticoagulant effect of Daparin in patients with ankle fractures and immobilized by casts. It was found that the incidence of DVT in the daparin anticoagulant group was 21% and 28% in the non-anticoagulant group. There was no statistical significance between the two groups and distal DVT was more common. Based on the higher incidence rate, the author suggested using other anticoagulant drugs. Lassen *et al.*[63] studied 371 patients with lower limb fractures or Achilles tendon ruptures treated in six hospitals in Denmark who were fixed with the cast for at least 5 weeks. They found that the incidence of DVT was 9% in the LMWH group and 19% in the placebo group, so they also recommended anticoagulant treatment. However, another study[64] involving several medical centers in the Netherlands came to the opposite conclusion. The study compared the effects of anticoagulation and non-anticoagulation in about 1500 patients with lower limb plaster fixation and concluded that the prevention scheme of LMWH was ineffective in the prevention of DVT. Data from a total of 6857 participants in 13 randomized trials showed that anticoagulants reduced the incidence of DVT in patients with temporary immobilization of the lower extremities when compared with untreated patients, but it also acknowledged that the personalized risk assessment of these patients may be the best choice to determine prophylactic anticoagulation[65]. Another study[66] by the same team came to a similar conclusion.

The main benefit of preventing thrombosis is to avoid fatal PE and symptomatic DVT. It is also very important to take precautions against asymptomatic DVT, which can reduce long-term complications, especially post-thrombotic syndrome (PTS), and bring benefits to patients. However, it is still recommended to assess the individual risk of DVT through the relevant rating scales, inform the patients of the risks and benefits, and finally decide whether to implement anticoagulant therapy based on patients' willingness and doctors' professional evaluation[67,68].

Prevention of Postthrombotic Syndrome May Be an Indication of Anticoagulation in Patients at High Risk for Proximal DVT or with Other Risk Factors

Postthrombotic syndrome (PTS) refers to the chronic venous dysfunction of the lower extremity which is secondary to DVT. It is generally characterized by swelling and pain, heaviness, pruritus, or pigmentation of the affected legs. Recurrent and intractable ulcers may occur in severe cases, and even after anticoagulant therapy of DVT, up to half of the patients developed into PTS within 2 years, and about 10% of them progressed to severe PTS. Due to the difficulty of treatment and the lack of long-term effect evaluation, once diagnosed, it will seriously affect the quality of life and increase the social and economic burden[69]. Therefore, the ACFAS believed that the avoidance of PTS should also be considered as an important endpoint for anticoagulation[56]. Prevention of DVT is a primary preventive measure for PTS, so DVT avoidance according to current guidelines can effectively prevent PTS[70]. Relevant literature[71,72] had identified the risk factors of PTS, including proximal DVT, previous ipsilateral DVT, primary venous insufficiency, aging, inflammation, such as high levels of inflammatory markers (C-reactive protein, intercellular adhesion molecule-1, and interleukin-6, etc.). Each factor above would increase the risk of PTS by two to three times, while prophylactic anticoagulation could prevent nearly 80% of PTS. Therefore, it is worth avoiding PTS for patients who broke legs at high risk of proximal DVT or with other risk factors.

The Outcome of Treatment for DVT

Up to now, there were few studies on the outcome of DVT treatment. Zhang *et al.*[73] followed up 140 patients over 60 years old with closed distal femoral fractures and found that the overall incidence of DVT was 35.0%, and the rate of distal and proximal DVT was 53.1% and 10.2%, respectively. After 3 months of anticoagulant therapy, 40.82% of distal DVT did not change and 16.3% of that was completely recanalized. In mixed DVT, 26.53% became distal

DVT, and 10.20% distal DVT developed into mixed type. It may seem as if the outcome of thrombosis after anticoagulation treatment for 3 months is satisfactory.

The Incidence of DVT in Upper Extremity Fractures May Not Be as Low as Previously Thought and Therefore Be Subject to Prophylactic Anticoagulation

It was thought that upper limb DVT was rare previously, but recent studies had shown that the incidence of upper limb DVT may not be as low as previously thought. Andrade *et al.*[74] studied 136 patients with DVT admitted to ICU in the past 5 years and found 75 (55.2%) cases of DVT were located in the upper limb, more than the lower extremity, and 6.7% of patients with upper extremity DVT had PE. Although DVT in the upper limb was more discovered, 14.8% of DVT in the lower limb developed PE in the end, which was higher than 6.7% of DVT in the upper limb. However, the study did not indicate the specific type of injury in each patient, so it was not possible to conclude whether this situation also applied to extremity fractures. Meanwhile, it was also possible that the author found more upper limb DVT by using more frequent ultrasound examinations than before, which was the so-called "more examination, more discovery"[75]. Johnson *et al.*[76] studied 1021 patients who had received intravenous ultrasound screening more than once during hospitalization. The results showed that the more examinations, the higher the incidence of distal DVT and the lower the incidence of PE, which had nothing to do with the incidence of proximal DVT, indicating that the more ultrasound examinations that occurred, the more the total incidence of DVT. A British guideline[77] stated that there was no evidence linking DVT with isolated upper extremity fractures, so prophylactic anticoagulation was not recommended. Other studies[78–81] had the same view. According to statistics, the incidence of DVT in patients with isolated upper extremity fractures was estimated to be 1%-5%, and there was no obvious increased risk in DVT during emergency surgery compared with elective surgery[82,83]. Therefore, the consensus view was that isolated upper extremity fractures did not need precautionary anticoagulation unless combined with higher risk factors.

The Incidence, Risk Factors, and Management Measures for DVT with Pediatric Fractures

Pediatric patients were defined from birth to 18 years old in the United States guidelines[84], and the incidence of DVT in children was much lower than that in adults. The incidence was slightly different from that reported by other countries, 5.3/10,000 in Canada, 0.14/10,000 in Holland, 0.07/10,000 in Britain, but the incidence of DVT with hospitalized children had increased significantly to 5-22/10,000[85]. The incidence of DVT in China[86] reported in children was 3.18/10,000. It was characterized by a bimodal distribution, the first was in infancy, accounting for 20%; then followed by adolescence, where approximately 50% of DVT occurred in children aged 11 to 18 years, and more in females than males. DVT in children was also dominated by deep veins in lower limbs, but the proportion of DVT in upper limbs was higher than that in adults, which might be related to the use of a central venous catheter (CVL)[87].

CVL is the most important risk factor for DVT in children. It was related to thrombosis accounts for 89% (Canada) and 94% (Netherlands). Other risk factors include sepsis, malignant tumor, immobilization, history of surgery, congenital heart disease, trauma, kidney disease, etc.[88–90]. Murphy *et al.*[91] reported that the incidence of DVT in children with lower limb fractures was 0.058%, and the most common sites related to DVT were femoral shaft and femoral neck fractures (40%), followed by tibia and ankle (34%), and pelvis (16%). The incidence of adolescents older than 12 was higher than that of infants and children. The overall mortality of children with DVT was very high, up to 9%–17%, but the mortality directly caused by DVT was low, about 1.5–2.2%[92].

A study[93] reported that only three cases of DVT were found in 2746 children under 16 years old with trauma. It was considered that the risk of thrombosis in children with trauma was low, so routine screening or preventive anticoagulant therapy was not recommended unless the patients needed long-term rehabilitation, accepted intravenous operation, or developed related clinical symptoms. Another study[94] found that the total incidence of DVT and PE in children with trauma was 0.08% (3/3637), and routine prevention was also not recommended. Only for children aged 9 or above, patients with initial GCS ≤ 8 or ISS ≥ 25, prophylactic measures should be considered. A study of 117,676 children by Georgopoulos[95] found that the incidence in the 14–17 age group was twice as high as that in the 0–13 age group, and aging, metabolic diseases, obesity, and implants increased the risk of DVT due to surgery.

Azu *et al.*[96] divided 13,880 patients into three groups according to age. The first group was younger than 13 years old, the second group was 13–17 years old, and the third group was older than 17-years-old. The first group did not receive any DVT prevention, the second group received surgery according to the doctor's decision whether to carry out anticoagulation, the third group received preventive anticoagulation measures. Results showed that no patients in the first group developed DVT, two patients in the second group developed DVT, and 59 patients in the third group developed DVT. After further analysis, the authors concluded that DVT prophylaxis was not required in trauma patients younger than 13 years of age, and there were no clear anticoagulant guidelines for adolescents aged 13–17 years old. Greenwald *et al.*[97] studied the incidence of DVT in 1782 children with pelvic and femoral fractures, 90% of whom were not treated with anticoagulant drugs. Results showed that only three patients (0.17%) developed DVT, and all of them occurred in children aged 15 years or above. In children under 14 years old, in particular, blood clot prevention might not be necessary. Sandoval *et al.*[98] analyzed the related risk factors of 358 children with DVT during 14 years period

and found that the most common risk factors of children with DVT before hospitalization were history of DVT or thrombotic diseases, while to hospitalized patients that included central catheter, especially femoral venous catheter, severe respiratory or tumor diseases, requiring long-term ICU treatment (average 12.7 days). The patients with the above risk factors need anticoagulant therapy.

Due to the age-dependent distribution, binding, and clearance of antithrombotic drugs, the antithrombotic treatment in children was different from that in adults. In addition, the incidence of children was relatively low, and there was still a lack of unified guidelines for the application of prophylactic anticoagulants. According to relevant literature[99], subcutaneous injection of 0.5 mg/kg low molecular weight heparin twice a day was adopted. Prophylaxis until be discharged from the hospital significantly reduced the incidence of DVT (by 65%).

In conclusion, anticoagulant therapy should be considered for children with one or more of the following risk factors: age > 13 years old, immobilization time >5 days, admitted to the ICU, with CVL, spinal fracture or spinal cord injury, complex lower extremity fracture, pelvic fracture requiring surgery or craniocerebral injury, previous DVT history, and complicated malignant tumor. Measures included physical methods such as LMWH administered according to body weight or sequential compression device[100].

The Choice and Complication of Inferior Vena Cava (IVC) for Patients with Anticoagulation Contraindications to Drugs

According to relevant guidelines[101], temporary or retrievable IVC filters were recommended for the following cases: patients with anticoagulant contraindication or with PE despite adequate anticoagulant treatment, patients with floating thrombosis in iliac or femoral veins, or patients with high-risk factors for acute VTE and planning pelvic or lower extremity surgery, etc.

IVC complications in descending order were filter migration, embolization, filter tilt, perforation, and rupture[102]. In summary, it is recommended that IVC filters be withdrawn as soon as indications disappeared (between 29 and 54 days after placement) to avoid complications and obtain the maximum clinical benefit.

The Earliest Safe Time to Start Drug Anticoagulation in Patients with Fractures Complicated with Solid Organ or Traumatic Brain Injury

Sagi *et al.*[103] had put forward some anticoagulant suggestions and guidelines for orthopaedic trauma patients by investigating 185 orthopaedic experts in North America and analyzing relevant literature and pointing out that patients with solid organ injury with stable hemodynamics could safely receive anticoagulant treatment after 24 h without continuous blood loss. For patients with closed craniocerebral trauma, if the neurological examination was not aggravated within 24–48 h, and continuous head CT scan showed that the condition was stable, anticoagulant treatment could be started after consulting the corresponding specialist.

In conclusion, through the untiring efforts of the countless sages of medicine, the causes, risk factors, prevention, and treatment of DVT have been well-understood till now, and the incidence is significantly lower than before. However, it is still the most common cardiovascular disease in the world after coronary heart disease and cerebrovascular disease, causing it to be the third-largest economic burden of disease in the world[104–106]. DVT is also a common complication in traumatic orthopaedic surgery. There have been specialized perioperative prevention guidelines for major orthopaedic surgery such as hip or knee replacement and hip fracture surgery. However, there is still a lack of global consensus or guidelines for other fracture types, which may need more evidence-based medicine support. In this study, by reviewing previous relevant literature, the above review is made on DVT problems that are clinically common in orthopaedic surgeons but have no consensus in the guidelines, which may be helpful to solve specific problems.

Summary

1. In isolated lower extremity fractures, the highest risk of preoperative DVT occurs in femoral fractures, mainly affecting injured extremity and distal DVTs; the closer to the distal extremity, the lower the incidence is. However, when multiple fractures or other risk factors are combined, the risk of DVT increases. The preoperative incidence of DVT at different fracture sites was shown in Table 1.
2. Current studies have shown that some readily available and inexpensive blood markers may indicate the risk of preoperative DVT for specific site fractures, but more evidence is needed. These indicators include platelet distribution width (PDW), high-density lipoprotein cholesterol (HDL-C), serum alkaline phosphatase (ALP), serum sodium concentration (Na^+), serum hydroxybutyrate

TABLE 1 The preoperative incidence of DVT at different fracture sites

Fracture types	Literature numbers	Cases of fractures	Incidence of preoperative DVT (%)
Femoral shaft fracture	16	2853	12.2–77.9
Fracture around knee joint	20	3520	9.0–52.5
Fracture of tibia and fibula	5	2358	2.86–28.65
Ankle fracture	9	337,537	0.28–14.6

Abbreviation: DVT, deep venous thrombosis.

TABLE 2 Blood indicators associated with preoperative DVT for fractures

Literature	Fracture types	Independent risk factors associated DVT
Ma[47]	Foot fracture (except calcaneal fracture)	PDW < 12%, HDL-C < 1.1 mmol/L, ALP > 100 U/L, Na^+ < 135 mmol/L
Ma[48]	Simple fracture of tibial shaft	HBDH > 182 U/L
Zhang[28]	Distal femur fracture	CRP > 11 mg/L, PLT > 217 × 10^9/L
Liu[31]	Tibial plateau fracture	Neutrophils > 5.02 × 10^9/L, PLT > 278 × 10^9/L
Luo[42] Duan[43]	Ankle fracture	ALB < 35 g/L, LYM < 1.8 × 10^9/L, D-dimer > 300 ng/ml
Tan[49]	Patellar fractures	LDL-C > 3.37 mmol/L, D-dimer > 4.5 ± 5.4 mg/L
Wu[50]	Femur and pelvis fractures	Anemia, hypoproteinemia
Qu[51]	Fracture around knee joint	D-dimer > 4.61 ± 3.34 mg/L
Temraz[52]	Multiple fracture types	Hyponatremia and hypernatremia

Abbreviations: ALB, albumin; ALP, alkaline phosphatase; CRP, C-reactive protein; DVT, deep venous thrombosis; HBDH, hydroxybutyrate dehydrogenase; HDL-C, high-density lipoprotein cholesterol; LDL-C, lipoprotein cholesterol; LYM, lymphocyte count; PDW, platelet distribution width; PLT, platelet.

dehydrogenase (HBDH), C-reactive protein (CRP), platelet (PLT), neutrophils, albumin (ALB), lymphocyte count (LYM), low-density lipoprotein cholesterol (LDL-C), fibrinogen degradation products (FDP), etc. Blood indicators associated with preoperative DVT for fractures was shown in Table 2.

3. The relevant expert consensus in China points out that for patients with femoral fractures, fractures around the knee, and multiple fractures far from the knee requiring surgery, considering the high risk of DVT, preoperative anticoagulation therapy is recommended, while for single fractures far from the knee, anticoagulation is not required unless associated risk factors are combined. For the above fracture types, if non-surgical treatment is adopted and immobilization is required for more than 4 weeks, it is recommended to fully explain the benefits and risks of preventive anticoagulant therapy to the patients, follow up the patients closely, and take anticoagulant therapy in time if necessary.
4. Due to the high incidence of PTS and the difficulty of treatment, patients with severe PTS can significantly affect the quality of life and increase the social and economic burden. Preventing DVT can effectively avoid PTS, therefore, it is recommended to consider the avoidance of PTS in patients at high risk for proximal DVT or in combination with one or more the following risk factors, such as the previous history of ipsilateral DVT, primary deep venous insufficiency, aging, and inflammatory status.
5. Currently, limited literature shows that nearly half of the distal DVT patients have no progress or improvement after 3 months of anticoagulant treatment, only about 10% of the distal DVT patients develop into mixed type, and about 1/4 of the mixed type DVT develop into distal type. Overall, the outcome at 3 months after the treatment of DVT is good.
6. The incidence of DVT in patients with isolated upper extremity fractures is low, and emergency surgery for upper extremity fractures is not associated with a significant increase in DVT compared to elective surgery. In conjunction with relevant guidelines, anticoagulation is not necessary for isolated upper limb fractures unless combined with a higher risk factor.
7. Anticoagulant therapy should be considered for children with one or more of the following risk factors: age >13 years, immobilization time >5 days, ICU treatment, central venous catheter implantation, spinal fracture or spinal cord injury, complex lower extremity fracture, pelvic fracture requiring surgery, combined with craniocerebral trauma, previous history of thrombosis or combined with a malignant tumor. DVT-related symptoms need to be closely observed or followed up, and thromboprophylaxis may be needed if necessary. Physical methods such as LMWH or sequential compression devices are recommended.
8. Temporary or retrievable IVC filter is recommended, and it should be removed in time if the indications disappear. The related complications include filter migration, embolism, filter tilt, perforation, and rupture.
9. For patients with fractures associated with solid organ injury, anticoagulant therapy can be initiated as early as 24 h if hemodynamics is stable. Patients associated with closed craniocerebral trauma may initiate prophylactic anticoagulation if the neurological examination and cranial CT do not worsen within 24 to 48 h. Re-consultation with the appropriate specialist is recommended.

Conflict of Interest

All the authors stated they had no conflict of interest.

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