

# Incidence and risk factors of preoperative venous thromboembolism in patients with malignant musculoskeletal tumors: an analysis based on D-dimer screening and imaging

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## Research Article

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## Abstract

**Background:** Venous thromboembolism (VTE) is a major complication in patients with malignant tumors and orthopedic disorders. Although it is known that patients undergoing surgery for orthopedic oncology are at an increased risk of thromboembolic events, only few studies have investigated this risk in detail. Therefore, the aim of this study was to determine the incidence and risk factors for preoperative VTE in orthopedic oncology patients.

**Methods:** We retrospectively reviewed the medical records of 270 patients who underwent surgical procedures, including biopsy for orthopedic oncology, have undergone measurements of preoperative D-dimer levels, and were subsequently screened for VTE by lower extremity venous ultrasonography and/or contrast-enhanced computed tomography scans. Statistical analyses were performed to examine the incidence and risk factors for VTE. Receiver operating characteristic (ROC) analysis was performed to verify the D-dimer cutoff value for the diagnosis of VTE.

**Results:** Overall, 199 patients (103 with primary soft tissue sarcomas, 38 with primary bone sarcomas, 46 with metastatic tumors, and 12 with hematologic malignancies) were included. D-dimer levels were high in 79 patients; VTE was detected in 19 patients (9.5%). Multivariate analysis indicated that age  $\geq 60$  years ( $P = 0.021$ ) and tumor location in the lower limbs ( $P = 0.048$ ) were independent risk factors for VTE. ROC analysis showed that the D-dimer cutoff value for the diagnosis of VTE was 1.53  $\mu\text{g}/\text{mL}$ ; the sensitivity and specificity were 89.5% and 79.4%, respectively.

**Conclusions:** Our study indicated that age and tumor location in the lower limbs were independent risk factors for preoperative VTE in orthopedic oncology patients. D-dimer levels were not associated with VTE in the multivariate analysis, likely because they are affected by a wide variety of conditions, such as malignancy and aging. Patients with high D-dimer levels and the identified risk factors are at an increased risk of preoperative VTE, and additional ultrasonography should be considered.

**Trial registration:** Our study was approved by the institutional review board. The registration number is B200600056. The registration date was July 13, 2020.

## Background

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major complication in orthopedic surgery. VTE is also known to be associated with malignancy, which increases the risk of VTE by 2- to 7-fold [1-3]. Several mechanisms may be involved in the promotion of thromboembolic events in cancer patients [4]. Because the risk of VTE is reported to be particularly high during the first few months after the diagnosis of malignancy [3], it is important to assess affected patients regarding this condition before initiating treatment.

D-dimer, the breakdown product of stabilized fibrin, is frequently used to screen for VTE as there is well-established evidence that levels below 0.5  $\mu\text{g}/\text{mL}$  have an exceedingly high negative predictive value

for the exclusion of PE [5-7]. Although lower extremity venography is the mainstay for the diagnosis of DVT, it has recently been replaced by lower extremity venous ultrasonography and contrast-enhanced computed tomography (CT) [8-10]. The combination of clinical symptoms, D-dimer concentrations, and contrast-enhanced CT has made it possible to diagnose 97.9% of VTE cases [11,12].

The incidence of perioperative VTE in orthopedic oncology patients ranges from 2.7% to 22% [13-21]. A myriad of factors, such as age, size and location of the tumor, chemotherapy, Ewing sarcoma family of tumors, metastases, pathological fracture, and type of surgery, have been suggested to be related to the occurrence of VTE [13-17,20-23]. However, most previous studies analyzed postoperative, rather than preoperative, patients who underwent orthopedic surgery [13,15-18,22]. In addition, routine screening for VTE was not considered; therefore, the reported rate of VTE represented only those that were clinically symptomatic [15,17].

Because such limitations may cause an underestimation of the incidence of VTE, only limited evidence is available for understanding preoperative VTE and associated risks for orthopedic oncology patients. Therefore, we investigated the incidence and risk factors for VTE in these patients and hypothesized that a combination of measuring D-dimer levels and imaging-based examination may be the best screening strategy for VTE.

## Methods

After obtaining approval from our institutional review board, we retrospectively reviewed the medical records of patients treated at our institution between January 2014 and June 2020. Out of 270 orthopedic oncology patients who underwent orthopedic surgical procedures, including open biopsy, and were assessed for preoperative VTE according to a flowchart developed by our institution, a total of 199 patients were included (Figure 1). VTE was screened by measuring preoperative D-dimer levels and subsequently performing lower extremity venous ultrasonography and/or contrast-enhanced CT. D-dimer levels were measured using a latex agglutination turbidimetric immunoassay; owing to the sensitivity of this assay, levels  $<0.50 \mu\text{g/mL}$  were considered  $0.50 \mu\text{g/mL}$ . Ultrasonography and CT scans were performed if the D-dimer level was  $\geq 1.0 \mu\text{g/mL}$ . In this study, DVT in the lower extremities that involved the popliteal vein or those above was defined as the proximal type; DVT involving the area below the popliteal vein was defined as the distal type. We excluded patients if they met any of the following criteria: benign condition; history of VTE; treatment with direct oral anticoagulants or heparin before the assessment of VTE; reoperation within 3 months; missing measurements of preoperative D-dimer levels; D-dimer levels  $\geq 1.0 \mu\text{g/mL}$ ; and missing lower extremity venous ultrasonography or contrast-enhanced CT examinations.

The clinical profiles of patients with VTE were retrospectively assessed. The anatomical location of the tumor was defined as the lower limb, including the pelvis, hip, thigh, knee, lower leg, ankle, and foot. Tumor location was also assessed based on the depth of the tumor. A soft tissue tumor located on the surface of the fascia was defined as superficial. Soft tissue tumors deeper than the fascia and bone

tumors were defined as deep. The patients comprised 103 men and 77 women, with a mean age of 60.9 years (range, 14–91 years). The tumor location was the lower limb in 133 patients. The tumors comprised 103 primary soft tissue sarcomas, 38 primary bone sarcomas, 46 metastatic tumors, and 12 hematologic malignancies. The pathological diagnoses of the patients are summarized in Table 1.

The Mann–Whitney test was used for continuous variables, and the chi-squared test or Fisher’s exact test were used for categorical variables. Logistic regression analysis was used for the multivariate analysis. Receiver operating characteristic (ROC) analysis was performed to verify the cutoff value of D-dimer for the diagnosis of VTE. Statistical significance was set at  $P < 0.05$ . All statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria).

## Results

The D-dimer concentration was  $\geq 1.0 \mu\text{g/mL}$  in 79 (39.7%) patients. The overall incidence of preoperative VTE detected by ultrasonography and contrast-enhanced CT scans was 9.5% (19 patients) (Table 2). VTE was detected in 8.7% and 7.9% of patients with soft tissue and bone sarcomas, respectively. The incidence of VTE in patients with metastases was 10.9%. Proximal VTE and PE were detected in 3 (2.5%) and 2 (1.7%) patients, respectively. The clinical profiles of the patients with VTE are summarized in Table 3. The patients comprised 10 men and 9 women with a mean age of 59.7 years (range, 19–91 years). The tumor was located in the lower limbs in 17 patients, accounting for 89.5% of the patients with VTE. The mean D-dimer level was  $2.64 \mu\text{g/mL}$  (range,  $1.05\text{--}11.72 \mu\text{g/mL}$ ). Among the patients with VTE, 9 had soft tissue sarcomas and 3 had bone sarcomas. The cases of soft tissue sarcoma included 4 cases of myxofibrosarcomas, 3 undifferentiated pleomorphic sarcomas (UPSs), and 2 leiomyosarcomas. The tumor was located on the surface of the fascia in 4 patients and deeper than the fascia in 5 patients. The cases of bone sarcoma included 2 UPSs of the bone and 1 osteosarcoma. Seven patients had bone metastases and hematologic malignancies. ROC analysis showed that the cutoff value of D-dimer for the diagnosis of VTE was  $1.53 \mu\text{g/mL}$ ; the area under the curve was 0.86, and the sensitivity and specificity were 89.5% and 79.4%, respectively.

The risk factors for VTE were analyzed using univariate analysis; we found that age ( $P = 0.0039$ ), age  $\geq 60$  years ( $P = 0.011$ ), tumor location in the lower limbs ( $P = 0.038$ ), and D-dimer levels ( $P < 0.001$ ) were associated with the incidence of VTE (Table 4). In contrast, sex, age, body mass index, size, origin, performance status, pathological fracture, and hematologic status, including hemoglobin, white blood cell, platelet, and C-reactive protein levels, were not identified as significant risk factors. Multivariate analysis indicated that age ( $P = 0.012$ ), age  $\geq 60$  years ( $P = 0.021$ ), and tumor location in the lower limbs ( $P = 0.048$ ) were independent risk factors for VTE. The D-dimer level was not significant in the multivariate analysis ( $P = 0.51$ ).

## Discussion

We investigated the incidence of preoperative VTE in orthopedic oncology patients. The most important finding in this study was that more affected patients could potentially have VTE than that reported by previous studies. In this study, VTE was detected in 19 of the 199 included patients (9.5%); the incidence was therefore higher than the rate of perioperative VTE reported in previous studies [13-18]. Several conditions in our study that differed from those in previous studies may have influenced the results. First, routine screening for VTE was performed. We performed DVT assessment in combination with routine D-dimer measurement, lower extremity ultrasonography, and contrast-enhanced CT scans. This screening strategy allowed for the diagnosis of patients with asymptomatic VTE. The necessity of anticoagulation therapy for these patients is controversial; however, Galanaud et al. reported that patients with cancer-related isolated distal DVT had a prognosis similar to that of patients with cancer-related isolated proximal DVT and a dramatically poorer prognosis than those with isolated distal DVT without cancer [24]. Therefore, for the management of preoperative orthopedic oncology patients, it is crucial to recognize that more patients have asymptomatic VTE than previously thought. Second, our study included patients with metastases and hematologic malignancies. The rate of DVT in surgical oncology patients receiving no prophylaxis was reported to be 35.2% [25]. The cancer type affects the incidence of VTE in adolescent and young adult patients; therefore, oncology patients, except for those with sarcomas, may have a different total incidence of VTE.

Several risk factors associated with an increased susceptibility of preoperative VTE in orthopedic oncology patients have been identified. Our study showed that increasing age and tumor location are independent risk factors. Age has been previously suggested to be associated with an increased risk of VTE [13,20]. Kim et al. reported an odds ratio of 5.84 in patients older than 60 years [13]. Our results showed a similar trend, and only two patients with VTE were younger than 60 years of age. Patients with bone or soft tissue sarcomas located in the hip or thigh have been suggested to have an increased risk of VTE [17]. Yamaguchi et al. demonstrated a high incidence of VTE (22%) in patients after resection of musculoskeletal tumors of the lower limb [20]. Since surgery involving the pelvis has been associated with the development of proximal DVT [22], patients with tumors in the lower limbs are suggested to be at an increased risk of VTE occurrence. In this study, 17 of 19 VTE patients had tumors in the lower limbs (89.5%), and the two VTE patients with tumors in the upper extremities were both older than 90 years of age.

Whilst the level of D-dimer showed an association with preoperative VTE in the univariate analysis, this was not confirmed in the multivariate analysis. This was likely due to the influence of increased age on D-dimer levels, as they need to be corrected by age, and the value of this fibrin degradation product itself should be evaluated carefully [5,7]. In addition, the D-dimer cutoff value in cancer patients was reported to be higher than that commonly used in clinical practice [26]. The cutoff value of D-dimer for the diagnosis of VTE was found to be 1.53 µg/mL in the present study, which was almost the same as that used for other cancer types [27,28]. The appropriate consideration of D-dimer limits the overuse and added cost of ultrasonography without a negative impact [29]. If D-dimer exceeds a level of 1.53 µg/mL, particularly in patients with the risk factors suggested in this study, additional assessment of VTE by lower extremity ultrasonography and contrast-enhanced CT should be considered.

Our study has several limitations. First, it was retrospective in nature and had a relatively small sample size. Some predictive variables may not have had sufficient statistical power; therefore, some important variables may have been ignored. Second, patients with metastases and hematologic malignancies were included. Regarding the evaluation of VTE risk in bone and soft tissue sarcoma patients, these malignancies should be evaluated in separate categories with sufficient sample sizes. Finally, lower extremity ultrasonography and contrast-enhanced CT for VTE evaluation were not unified.

## Conclusion

Our study indicated that age and tumor location in the lower limbs were independent risk factors for preoperative VTE in orthopedic oncology patients. D-dimer levels were not identified as independent risk factors in the multivariate analysis because it is affected by a wide variety of conditions, including malignancy and aging. Nevertheless, this measure was useful for exclusion diagnosis because of its high sensitivity. Patients with high D-dimer levels and the identified risk factors are at an increased risk of preoperative VTE and should be considered for additional assessment.

## Abbreviations

Abbreviations	Full spelling
CT	computed tomography
DOAC	direct oral anticoagulant
DVT	deep vein thrombosis
PE	pulmonary embolism
ROC	receiver operating characteristic
VTE	venous thromboembolism

## Declarations

**Ethics approval and consent to participate:** This research has been approved by the IRB of the Yokohama City University Hospital. The approval number is B200600056. All methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from all participants or, if participants are under 16, from a parent and/or legal guardian.

**Consent for publication:** Consent for publication was obtained from all participants or, if participants are under 16, from a parent and/or legal guardian.

**Availability of data and materials:** Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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**Authors' contributions:** K.H. was a major contributor in writing the manuscript. Y.K. have made design of the work. K.S. analyzed the patient data. S.F. interpreted the patient data and prepared Table 1-2. I.K. was a major contributor in pathological assessment. H.C. and M.T. have made substantial contributions to the conception. Y.I. have approved the submitted version. All authors read and approved the final manuscript.

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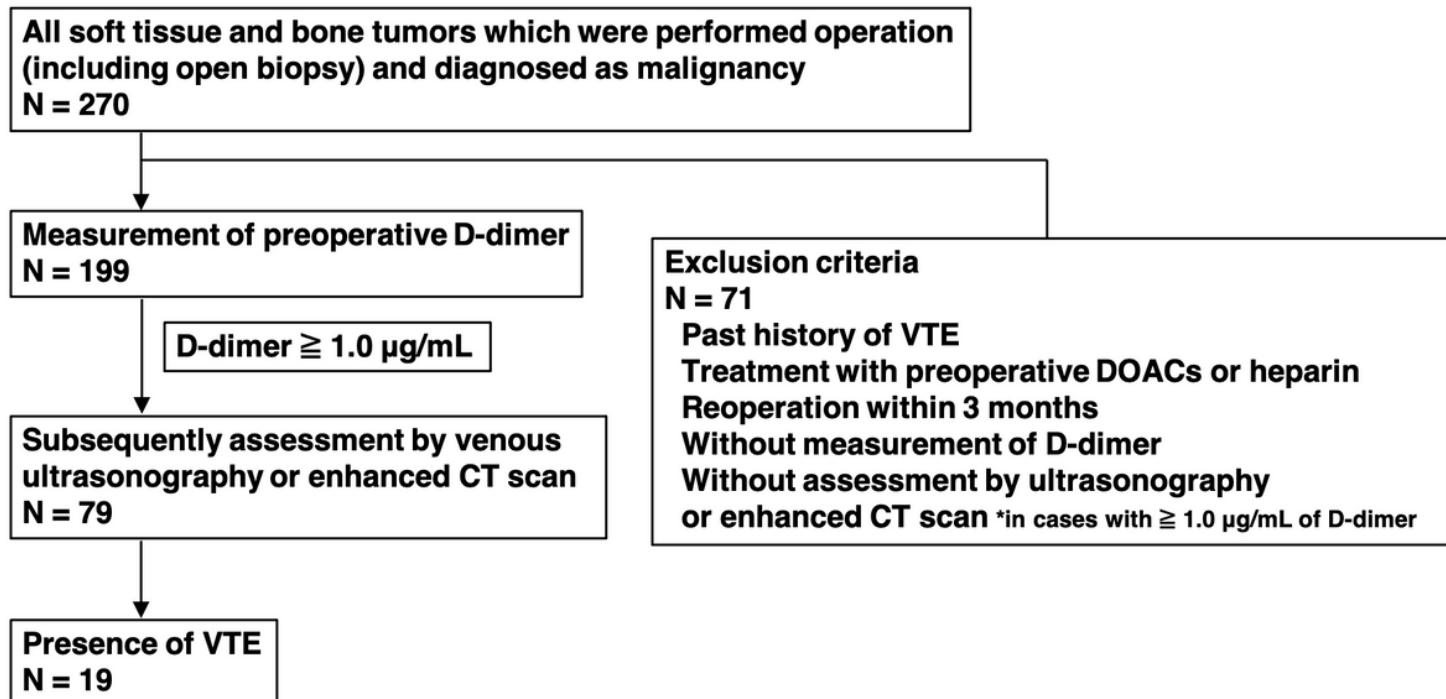
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## Tables

Due to technical limitations, Tables 1,2,3 and 4 are only available as a download in the Supplemental Files section.

## Figures



## **Figure 1**

Flow chart depicting the venous thromboembolism assessment strategy. Patients were evaluated using D-dimer screening, lower extremity venous ultrasonography, and contrast-enhanced computed tomography. A total of 71 patients were not included based on the exclusion criteria. CT: computed tomography; VTE: venous thromboembolism.