Original Article

Preoperative Chemotherapy, Previous Deep Vein Thrombosis/Pulmonary Thromboembolism, and Old age are Predictors of Preoperative Deep Vein Thrombosis

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ABSTRACT

Background: The purpose of this study was to identify predictors for preexisting thrombi before surgery so that a decision can be made as to the advisability of intermittent pneumatic compression, which is contraindicated in patients with thrombi, among the methods to prevent perioperative deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE).

Methods: Plasma D-dimer was measured preoperatively in 521 consecutive patients aged ≥20 years who underwent elective surgery. With a D-dimer level ≤0.72 μg/mL, thrombi were considered absent. With a D-dimer level >0.72 μg/mL, lower limb venous ultrasonography was performed, and the presence/absence of thrombi was recorded. Multivariate logistic regression analysis was performed with presence/absence of thrombi as the response variable and predictors for DVT as explanatory variables.

Results: After excluding 14 patients in whom lower limb venous ultrasonography could not be performed because of fractures or skin lesions, the analysis included 507 patients. The *p* values for chemotherapy, previous DVT/PTE, and for age were <0.05. On receiver operating characteristic curve analysis with age, the threshold value at which the sum of sensitivity and specificity was the largest was 64 years. When patients with age ≥65 years, chemotherapy, or previous DVT/PTE were assumed to have thrombi, the positive predictive value was 0.14 and the negative predictive value was 0.99. Among patients with one or more of these three factors, 27 patients had actual thrombi; additionally, 22 of the 27 patients had no restrictions on daily living.

Conclusions: Chemotherapy, previous DVT/PTE, and old age are predictors of preoperative DVT.

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KEYWORDS: preoperative deep vein thrombosis, prediction, intermittent pneumatic compression, D-dimer, lower limb venous ultrasonography

Deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE) are serious perioperative complications that need to be prevented. Among surgical patients for whom anticoagulants are contraindicated, intermittent pneumatic compression (IPC) is an effective means of preventing DVT of the lower limbs,[1,2] but it is contraindi-

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cated when thrombi exist in the veins of the lower limbs because of the possibility that the thrombi will become dislodged by IPC and cause PTE.

Although D-dimer is widely used for DVT screening because of its high sensitivity and negative predictive value, diagnostic imaging is necessary to confirm the diagnosis of DVT because of its low specificity and positive predictive value.[3] Because of this, even if the D-dimer value is high, lower limb venous ultrasonography and/or venography are needed to evaluate the presence or absence of thrombi prior to performing IPC, but performing these procedures in all patients during the preoperative period is not practical. Two studies have investigated the presence or absence of thrombi in the lower limbs with venous ultrasonography and venography and predictors for the presence of DVT. The study of Wells et al.[4] took symptomatic patients as subjects and is thus not applicable to the asymptomatic lower limb venous thrombosis that is more common in the preoperative period. In the study of Gearhart et al.[5] the subjects were trauma patients, and their findings are therefore not applicable to non-trauma patients.

In the guidelines for venous thromboembolism prevention by the American College of Chest Physicians (ACCP),[6,7] multiple risk factors for DVT/PTE are given, but no studies have analyzed the contributions of these factors to the formation of lower limb venous thrombosis in the preoperative period.

Since there was no established preoperative DVT predictor, it was not possible to determine whether the IPC, which could cause VTE by dislodging thrombi, should be used for perioperative thrombosis prevention without lower limb venous ultrasonography. In addition, it is necessary to reduce the number of patients undergoing lower limb venous ultrasonography, because DVT is suspected in a relatively large number of patients by D-dimer screening. We, thus, conducted this study to investigate the predictors of preoperative lower limb DVT in adult patients undergoing elective surgery.

Materials & Methods

This prospective observational study was approved by the ethics committee of Toho University Sakura Medical Center and was conducted with written, informed consent from the participating patients (protocol No. 2008-005, 2008-27).

The participants were 521 consecutive patients aged 20 years or older who underwent elective surgery at Toho University Sakura Medical Center from November 12, 2008, to April 18, 2009.

Plasma D-dimer was measured with latex photometric immunoassay (LPIA). A level of $\leq$0.72 μg/mL, the limit of the normal range, was taken to indicate that no DVT was present. Levels of $>$0.72 μg/mL were taken to indicate possible DVT, in which case lower limb venous ultrasonography was performed, and the presence or absence of DVT was recorded.

The anesthesiologist in charge recorded whether risk factors for DVT/PTE were present in all subject patients. The recorded DVT/PTE risk factors were in accordance with the Guidelines for Venous Thromboembolism Prevention, 8th Ed., by the ACCP,[6] but to avoid variability in the records among the individual anesthesiologists, "immobility" was redefined as "bed confinement for $\geq$3 days within the past 4 weeks," and "venous compression" was defined as "obvious venous compression on diagnostic images and/or pelvic mass with a diameter of $\geq$10 cm." "Obesity" was analyzed with body mass index as a continuous variable, and "increasing age" was analyzed with age as a continuous variable (Table 1).

Multivariate logistic regression analysis was performed with the presence or absence of thrombi as the response variable and DVT/PTE risk factors as explanatory variables. Items for which the p value was less than 0.05 with respect to the null hypothesis of a regression coefficient of 0 were selected as significant predictors. When a selected item was a continuous variable, it was evaluated by receiver operating characteristic (ROC) curve analysis only for the purpose of simplifying the prediction equation by converting to a categorical variable with the threshold value at which the sum of sensitivity and specificity was the largest. A 2 × 2 contingency table of the presence or absence of actual thrombi and the presence or absence of thrombi presumed when one of the risk factors was positive was prepared, and sensitivity, specificity, positive predictive value, negative predictive value, predictive accuracy, and the error rate were calculated.

Since an appropriate sample size could not be identified from an extensive reading of previous reports, the sample size was determined with the following method. Given that the smaller of the number of outcome carriers and noncarriers is thought to have to be at least 10 times greater than the number of explanations used in the model,[8] if the explanatory variable is narrowed to five

Table 1 Risk factors given in the Guidelines for VTE Prevention, 8th ed., by the ACCP, and risk factors examined in the present study

Risk factors in the Guidelines for VTE Prevention, 8th ed., by the ACCP	Risk factors examined
Surgery	-
Trauma (major trauma or lower extremity injury)	Major trauma Lower extremity injury
Immobility, lower extremity paresis	Bed confinement for ≥3 days within the past 4 weeks Lower extremity paresis
Cancer (active or occult)	Cancer
Cancer therapy (hormonal, chemotherapy, angiogenesis inhibitors, radiotherapy)	Cancer therapy (hormonal, chemotherapy, angiogenesis inhibitors, radiotherapy)
Venous compression (tumor, hematoma, arterial abnormality)	Obvious venous compression on diagnostic images and/or pelvic mass with diameter ≥10 cm
Previous VTE	Previous DVT/PTE
Increasing age	Age
Pregnancy and the postpartum period	Pregnancy and the postpartum period
Estrogen-containing oral contraceptives or hormone replacement therapy	Estrogen-containing oral contraceptives or hormone replacement therapy
Selective estrogen receptor modulators	Selective estrogen receptor modulators
Erythropoiesis-stimulating agents	Erythropoiesis-stimulating agents
Acute medical illness	Acute medical illness
Inflammatory bowel disease	Inflammatory bowel disease
Nephrotic syndrome	Nephrotic syndrome
Myeloproliferative disorders	Myeloproliferative disorders
Paroxysmal nocturnal hemoglobinuria	Paroxysmal nocturnal hemoglobinuria
Obesity	Body mass index
Central venous catheterization	Central venous catheterization
Inherited or acquired thrombophilia	Inherited or acquired thrombophilia

VTE: venous thromboembolism, ACCP: American College of Chest Physicians, DVT: deep vein thrombosis, PTE: pulmonary thromboembolism

items, at least 50 patients with thrombi are needed. Asymptomatic DVT/PTE in general surgery patients is thought to be present in from 10-20% to 15-40%[6]; therefore, the incidence of asymptomatic DVT in preoperative patients is probably lower. Assuming an incidence rate of 5%, this study was started with a goal of 1,000 preoperative patients. From an interim analysis at the point when more than 500 patients were accrued, whether this study should continue was considered.

All statistical analyses were performed with EZR version 1.31 for Windows (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.[9]

Results

Among patients with D-dimer >0.72 μg/mL, lower limb venous ultrasonography could not be performed in 11 patients in the lower extremity injury group because of cast immobilization, traction immobilization, and pain and in 3 patients because of leg skin defects or ulcers. After excluding these 14 patients, the analysis was done with 507 subjects. Of these 507 patients, D-dimer was ≤0.72 μg/mL in 326, all of whom were assumed to have no DVT. Of the 181 patients with D-dimer levels >0.72 μg/mL and in whom lower limb venous ultrasonography could be done, DVT was discovered in 31. The flow diagram for patient exclusion and determining the presence or absence of thrombi is shown in Fig. 1.

Of the risk factors, there were no patients with major trauma, selective estrogen receptor modulators, erythropoiesis-stimulating agents, acute medical illness, nephrotic syndrome, myeloproliferative disorders, paroxysmal nocturnal hemoglobinuria, central venous catheterization, or inherited or acquired thrombophilia, and so these were excluded from the analysis. Analysis could not

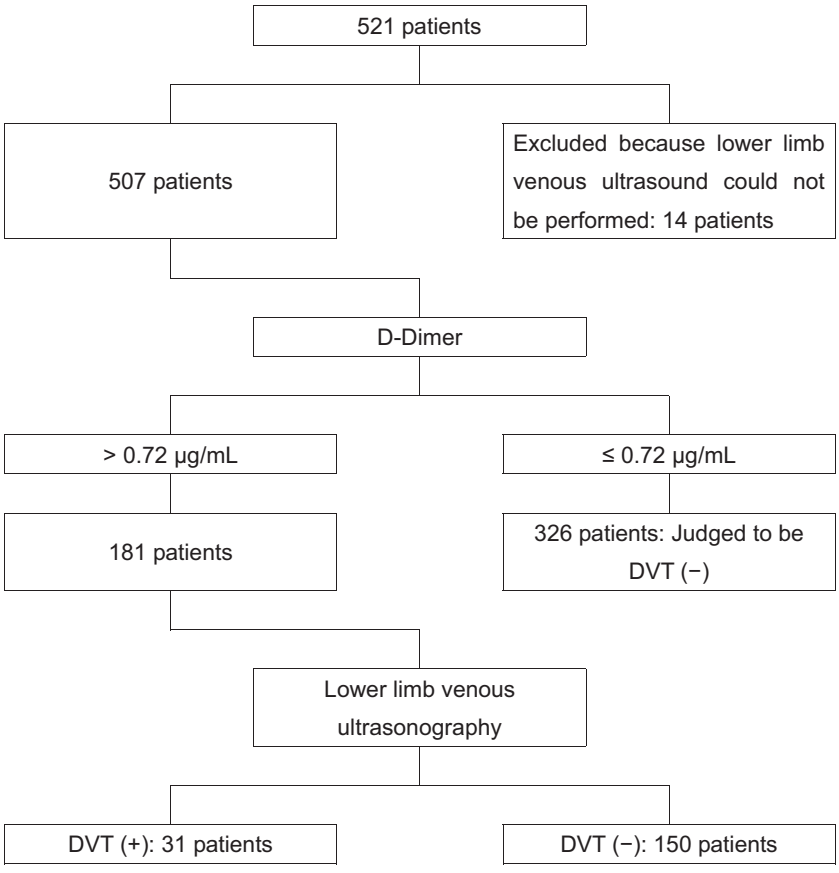

Fig. 1 Diagram showing patient flow and the determination of the presence or absence of thrombi

be done in 11 of the total of 18 patients with lower extremity injury, and so lower extremity injury was excluded from the analysis.

The clinical characteristics of the cancer cohort are shown in Table 2. The proportion of patients was 11.7%, 41.4%, 17.9%, 31.0%, and 15.2% in stages 0, I, II, III, and IV, respectively. The cancer therapy was chemotherapy in all cases. There were no postpartum patients, and so all "pregnancy and the postpartum period patients" were patients who were pregnant. In venous compression patients, there were none in whom obvious venous compression was seen on diagnostic imaging; all were patients with a pelvic mass ≥10 cm in diameter. Among all patients, there were none with a Hugh-Jones classification ≥3, and there was one patient with a New York Heart Association (NYHA) Functional Classification ≥3. The numbers of patients taking anticoagulants and/or antiplatelet agents before surgery are shown in Table 3.

Table 4 shows the results of a multivariate logistic regression analysis. In this analysis, presence or absence of thrombi was taken as the response variable, and the risk factors for DVT were taken as explanatory variables. The factors for which the p value was less than 0.05 were age, cancer therapy, and previous DVT/PTE. There were 31 patients with actual thrombi, and three risk factors were identified as predictors. Therefore, it was thought valid to conclude the study at this point.

Since age is a continuous variable, an evaluation was done with ROC curve analysis. The sum of sensitivity and specificity was found to be largest at the age of 64 years (Fig. 2).

There were 197 patients who had at least one of the three risk factors: cancer therapy, previous DVT/PTE, and age ≥65 years. Among them, the number who actually had a thrombus was 27 (Table 5). Accordingly, when these three factors were taken as predictors for preoperative DVT, the sensitivity was 0.87, specificity was 0.64, the positive predictive value was 0.14, predictive accuracy

Table 2 Clinical characteristics of the cancer cohort

Cancer type	Number of patients	Stage					
		0	I	II	III	IV	Unknown
		Number of patients (patients with actual thrombi)					
Gastric	26	1 (0)	13 (0)	5 (1)	4 (0)	3 (0)	
Colorectal	37	7 (0)	9 (0)	5 (1)	9 (2)	7 (2)	
Lung	10	0 (0)	6 (0)	0 (0)	3 (1)	1 (0)	
Breast	24	0 (0)	10 (0)	12 (1)	2 (0)	0 (0)	
Uterine	13	5 (0)	7 (0)	0 (0)	0 (0)	1 (0)	
Ovarian	9	0 (0)	3 (0)	1 (0)	1 (0)	4 (1)	
Bladder	9	4 (0)	5 (0)	0 (0)	0 (0)	0 (0)	
Other	17	0 (0)	7 (1)	3 (1)	0 (0)	6 (2)	1 (0)
Total	145	17 (0)	60 (1)	26 (4)	19 (3)	22 (5)	1 (0)

Table 3 Numbers of patients taking anticoagulants and/or antiplatelet drugs before surgery

	DVT (+) group n = 31	DVT (−) group n = 476
	Number of patients	
Aspirin	1	9
Aspirin and cilostazol	1	0
Aspirin, cilostazol, and limaprost alfadex	0	1
Aspirin and clopidogrel	0	1
Aspirin and ticlopidine	0	2
Cilostazol	1	0
Limaprost alfadex	0	1
Warfarin	1	3
Warfarin and cilostazol	0	1
Total	4	18

DVT: deep vein thrombosis, DVT (+) group: patients with actual thrombi, DVT (−) group: patients with D-dimer $\leq$0.72 μg/mL (n = 326) and patients in whom no thrombi were detected by lower limb ultrasonography (n = 150)

was 0.66, and the error rate was 0.34. Among the 27 people with actual thrombi, 5 patients had one of the risk factors of NYHA Functional Classification >2, bed confinement, or paralysis, while 22 patients had thrombi despite leading a regular life.

Discussion

The results of this study suggest that the three factors of previous DVT/PTE, chemotherapy, and old age are useful predictors of preoperative DVT.

The Guidelines for Venous Thromboembolism Prevention in Nonsurgical Patients, 9th Ed, by the ACCP,[10] cover nonsurgical inpatients, who are thought to be close to the patients in this study. The guidelines introduce several risk assessment models (RAMs),[11–13] and previous DVT/PTE, chemotherapy, and old age, which were suggested as predictors of preoperative DVT in the present study, are all included in these RAMs.

On the other hand, cancer, which has been included as a high DVT/PTE risk factor in multiple RAMs,[11–13] was not among the predictors in this study. This is thought to be because the majority of the cancer patients in this study had early stage cancer of 0-I (Table 2), and, unlike other studies whose subjects were acutely ill, hospitalized medical patients,[11–13] the present subjects were preoperative patients for elective surgery in whom systemic hypercoagulability is not thought to have occurred. In an American cohort of 208,200 surgical individuals, Reinke et al. reported that the relative risk of cancer on DVT/PTE increased comparing benign and carcinoma *in situ* neo-

Table 4 Presence of DVT by each risk factor

	DVT (+) group n = 31	DVT (−) group n = 476	Multivariate analysis		p-value
			Odds ratio	95% CI	
Sex					
Male	15 (51.6%)	203 (57.4%)	0.576	0.224-1.48	0.254
Female	16 (48.4%)	273 (42.6%)			
Age (years)	71 ± 8.38	53 ± 17.12	1.08	1.04-1.13	3.83×10^{-4} *
BMI (kg/m^2)	21.8 ± 3.13	22.8 ± 3.90	0.966	0.862-1.08	0.55
Immobility	4 (12.9%)	20 (4.2%)	0.864	0.151-4.94	0.869
Lower extremity paresis	2 (6.5%)	3 (0.6%)	4.12	0.332-51.1	0.271
Cancer	13 (41.9%)	131 (27.5%)	0.857	0.296-2.48	0.775
Cancer therapy	8 (25.8%)	12 (2.5%)	9.76	2.39-39.9	0.0015 *
Venous compression	0 (0%)	20 (4.2%)	2.05×10^{-7}	0-Inf	0.995
Previous DVT/PTE	10 (32.3%)	3 (0.6%)	30.6	6.70-140	1.02×10^{-5} *
Pregnancy and the postpartum period	0 (0%)	18 (3.8%)	7.76×10^{-7}	0-Inf	0.996
Estrogen-containing oral contraceptives or hormone replacement therapy	0 (0%)	17 (3.6%)	2.76×10^{-7}	0-Inf	0.995
Inflammatory bowel disease	1 (3.2%)	20 (4.2%)	3.56	0.38-33.5	0.266

Numbers of cases are shown with percentages in brackets. Values are expressed as means ± standard deviation for continuous variables.

DVT: deep vein thrombus, PTE: pulmonary thromboembolism, DVT (+) group: patients with actual thrombi, DVT (−) group: patients with D-dimer ≤0.72 μg/mL (n = 326) and patients in whom no thrombi were detected by lower limb ultrasonography (n = 150), BMI: body mass index, Inf: infinity, *: $p < 0.05$

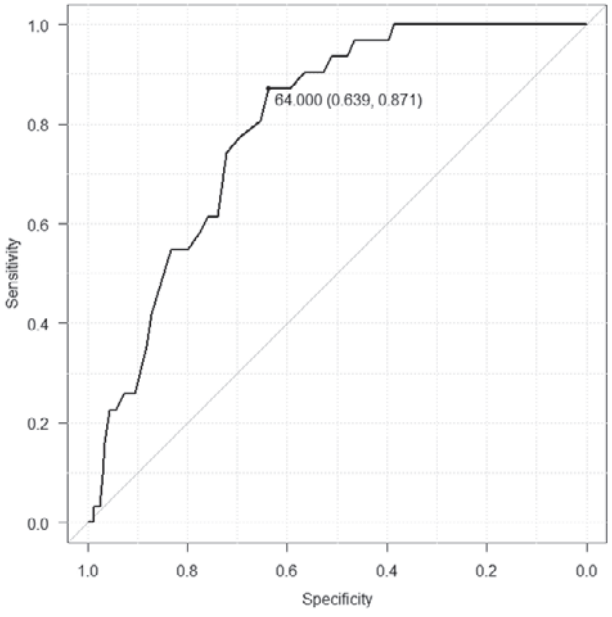

Fig. 2 Receiver operating characteristic (ROC) curve analysis for age as a predictor for DVT
The vertical axis shows sensitivity, and the horizontal axis shows specificity. At the age of 64 years, the sum of sensitivity and specificity is the largest.
DVT: deep vein thrombosis

plasms,[14] namely, cancer stage 0. In a Danish cohort of 57,591 individuals with cancer hospitalized for VTE, Cronin-Fenton et al. described that the incidence rates of VTE were highest in individuals with cancer of the pancreas, brain, liver, multiple myeloma, and any form of advanced-stage cancer.[15] Although there is no large-scale research for the effect of cancer stage on preoperative DVT, it seems that these researches suggested that early stage cancer does not increase the risk of preoperative DVT. Another reason may be that evaluation (i.e., plasma D-dimer measurement and lower limb venous ultrasonography) was performed before admission or during the very short period of hospitalization. A re-examination with patient groups diverse enough to allow judgment of risk by stage is desirable.

With regard to immobility as well, while a high risk of DVT/PTE has been found in acutely ill, hospitalized medical patients,[11–13] it was not found to be a predictor in the present study. In an evaluation of risk factors for DVT/PTE in 15,156 hospitalized medical patients, Spyropoulos et al. identified immobilization, which was defined as confinement to a bed or chair, ≥7 days as one of the independent risk factors,[12] but in the present study, the criterion for immobility was ≥3 days. Barber et al. conducted a prospective cohort study evaluating a RAM to identify patients with DVT/PTE risk among 1,180 hospitalized medical patients, and they gave the highest score of 3 to previ-

Table 5 Contingency table with cancer therapy, previous DVT/PTE and age ≥65 years as predictors

	Predicted DVT (+)	Predicted DVT (−)	Total
Actual DVT (+)	27	4	31
Actual DVT (−)	170	306	476
Total	197	310	507

Sensitivity: 27/31 = 0.87
Specificity: 306/476 = 0.64
Positive predictive value: 27/197 = 0.14
Negative predictive value: 306/310 = 0.99
Predictive accuracy: (27 + 306)/507 = 0.66
Error rate: (4 + 170)/507 = 0.34
DVT: deep vein thrombosis
PTE: pulmonary thromboembolism

ous DVT/PTE, active cancer, and "reduced mobility",[13] but while their definition of this was bed rest with bathroom privileges, which was due to either patient's limitations or on physician's order, for at least 3 days, immobility in the present study was defined as bed rest and did not include bathroom privileges. Moreover, the patients in these previous studies were acutely ill, hospitalized medical patients, whereas the subjects in the present study were preoperative patients for elective surgery. Thus, we suppose that immobility was not identified as a predictor in the present study because of the different definitions of immobility and the different characteristics of the patients evaluated. Immobility could have been identified as a predictor of preoperative DVT if prolonged period or bathroom privileges had been included in the definition.

An already known thrombophilic condition was similarly found to be a high risk, but it was not a subject of analysis in the present study. Tests for antithrombin, protein C, protein S, factor V Leiden, G20210A prothrombin mutation, and antiphospholipid antibody syndrome are not generally included in routine examinations during the preoperative period. When these tests become less expensive and easier to perform, they should be added to the preoperative examinations.

Since cancer therapy was chemotherapy in all cases in the present study, hormone therapy and radiation therapy could not be evaluated. In addition, there were no patients with risk factors of major trauma, erythropoiesis-stimulating agents, nephrotic syndrome, myeloproliferative disorders, paroxysmal nocturnal hemoglobinuria, central venous catheterization, inherited thrombophilia, and acquired thrombophilia in the present study. Thus, these risk factors could not be evaluated. Moreover, patients undergoing emergency surgery were not included in this study; therefore, the study results cannot be applied to emergency cases.

In patients with lower limb fractures, evaluation could not be performed because of cast or traction immobilization and pain. However, the presence of lower limb fractures is already recognized to be a strong risk factor for perioperative DVT/PTE, and in many cases, anticoagulant therapy is given to prevent DVT/PTE. There is not a great need to inquire into the advisability of IPC, a physical therapy that substitutes for anticoagulant therapy, in these patients.

Because the patients who underwent venous ultrasonography in this study were screened with D-dimer, it is possible that there were some thrombus patients in whom venous ultrasonography was not done. D-dimer, however, has been widely used for screening and diagnosis of DVT/PTE[16] and was included in the diagnostic algorithm of the "Guidelines for the Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis."[17] The guidelines also stated that "Patients with abnormal D-dimer levels should be evaluated with imaging techniques to confirm the diagnosis. Physicians should be aware that the presence of normal D-dimer levels can exclude acute-phase DVT but cannot exclude chronic-phase DVT."[17] Because the purpose of this study was to identify predictors for acute-phase DVT that could be dislodged by IPC, the methodology of excluding acute-phase DVT by normal D-dimer levels was considered acceptable. With regard to the D-dimer threshold, we were unable to find studies to serve as a reference; therefore, the value of 0.72

μg/mL was adopted, since the upper limit of the 95% confidence interval obtained from the measured values of 115 healthy adults was 0.7182 μg/mL (unpublished company data, Mitsubishi Chemical Medience Corp., Tokyo, Japan). Nomura et al. took a cutoff value of 1.2 μg/mL to obtain the 100% negative predictive value of DVT/PTE from LPIA-D-dimer among patients who were suspected of having some type of thrombosis.[18] Matsuo et al. took a cutoff value of 0.9 or 1.0 μg/mL to obtain the 100% negative predictive value of DVT/PTE from D-dimer among hospitalized patients identified as high risk of developing DVT/PTE regardless of whether it is symptomatic or asymptomatic.[19] Therefore, the threshold of 0.72 μg/mL in the present study seems reasonable. However, in order to assert the results of this study, it may be necessary to confirm that there is no DVT if D-dimer <0.72 in the asymptomatic patients and/or patients with low risk factors.

Whether a thrombus is new or old is a major factor in determining the treatment strategy at the stage when the thrombus is discovered. Thrombi become harder and more calcified with time after they develop, and so evaluation of their freshness with ultrasonography is done on the basis of whether they have elasticity and calcification. Stiffness can be assessed semiquantitatively with an elastography function of the ultrasonic diagnostic equipment, which expresses tissue stiffness with color.[20] Unfortunately, some devices in our hospital do not have the elastography function. Thus, evaluation of thrombi with elastography was not included in the present study. In venous thrombi that were generated experimentally, calcification was found to develop on the ninth day after thrombus generation.[21] It seems, therefore, uncertain whether a thrombus can be judged to be old from the presence or absence of calcification.

Since sensitivity for thrombi in patients with extracted predictors was sufficiently high at 0.87, lower limb venous ultrasonography should be performed to confirm the presence or absence of thrombus before surgery if IPC is selected for the prevention of DVT.

On the other hand, it is difficult to assume that there is no DVT unless the patient has one of three predictors. Because the number of samples in this study was not sufficiently large, there is no guarantee that equivalent conclusions can be drawn in any kind of patients groups. D-dimer screening should be performed; thereafter, lower limb venous ultrasonography should be applied for patients with predictors enumerated in guidelines or RAMs and patients with a D-dimer level higher than the threshold. However, results in this study suggest that it is possible to consider that lower limb venous ultrasonography could be cut down to the patients with preoperative chemotherapy, previous DVT/PTE, or age ≥ 65 years.

The additional interesting finding in the present study was that of the 27 preoperative DVT patients who had one of the predictors of chemotherapy, previous DVT/PTE, or age ≥ 65 years, 5 patients had NYHA Functional Classification >2, bed confinement, or paralysis, while 22 patients had thrombi despite leading a regular life. The underlying mechanism of the physical method of thrombus prevention is to mimic the blood flow increase caused by muscle pumps during walking. Thus, we suppose that the physical method may not decrease the perioperative risk of thrombus formation in patients who have thrombi even though they lead a regular life. Therefore, we supposed that the first choice for perioperative thrombus prevention might be anticoagulant therapy for patients with the predictors of chemotherapy, previous DVT/PTE, or age ≥ 65 years, if the risk of bleeding complication is assumable to be low.

Conclusion

In elective surgery of patients aged ≥ 20 years, the factors of preoperative chemotherapy, previous DVT/PTE, and age ≥ 65 years were predictors for preoperative DVT.

Conflicts of interest: The authors have no conflicts of interest to disclose.

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