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Original

D-dimer Measurement for Prediction of Pre- and Post-operative Venous Thromboembolism in General and Abdominal Surgical Cases

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The significance of D-dimer testing for venous thromboembolism (VTE) screening and risk assessment was reviewed by comparing preoperative D-dimer levels and Caprini score. This study involving general and abdominal surgery patients was performed in our department over a 1-year period. In order to screen for preoperative VTE, D-dimer levels were measured in 307 patients. The 82 patients with high D-dimer levels (>1 μg/mL) or with a past or family history of VTE underwent venous duplex scanning and enhanced computed tomography. Pre-operative VTE was detected in 12 patients, and the overall prevalence of VTE was 3.9%. For individual VTE risk assessment, Caprini score was derived for all 307 patients. Average Caprini score was 6.83 (± 2.04) for VTE-positive cases and 5.54 (± 1.75) for VTE-negative cases. Prevalence of VTE increased with increasing Caprini score ($p = 0.0238$). Caprini score is thus effective for VTE risk stratification. Average Caprini score was 5.53 (± 1.86) in the high D-dimer group and 4.74 (± 1.90) in the low D-dimer group. Caprini score increased with increasing D-dimer level ($p = 0.0006$). Preoperative D-dimer testing may thus be useful not only to screen for preoperative VTE, but also to assess VTE risk.

Key Words: Caprini score, D-dimer, general and abdominal surgery, venous thromboembolism

Introduction

Deep vein thrombosis (DVT) is the most common cause of pulmonary thromboembolism (PTE). In fact, PTE and DVT are collectively referred to as venous thromboembolism (VTE) due to their close correlation[1].

In Western countries, VTE is the third most common cause of cardiovascular disease after heart attack and stroke, and its pathology and treatment have been studied in detail[2]. On the other hand, since the incidence of this pathology has been considered relatively low in Japan[3)~5)], there has been no focus on VTE. However, the incidence of VTE has recently been increasing[6)7)], and this pathology has therefore been gaining attention. A 2006 study showed that the incidence of postoperative VTE in Japan was equivalent to that in Western countries[8].

Recent VTE incidents include the first Japanese case of death due to PTE[9] and major media coverage of "economy class syndrome". Given such circumstances, interest in VTE is growing in Japan. Furthermore, a system for preventing and managing VTE was established in line with revisions to the medical payment system by the Ministry of Health, Labour and Welfare in April 2004, and the Japanese Guideline for Prevention of Venous Thromboembolism[1], based on the 6th American College of Chest Physicians (ACCP) guideline[10], by the Editional Committee on Japanese Guideline for Prevention of Venous Thromboembolism and the Japanese Circulation Society in the same year. Compared with 2002-2003 data prior to the announcement of the guideline, results of the 2009-2011 study showed that both the incidence and mortality rate of perioperative PTE were declining[11]. However,

Table 1 Caprini risk assessment model and VTE risk level based on Caprini score in general and abdominal surgery patients

1 Point	2 Points	3 Points	5 Points
Age 41-60 y	Age 61-74 y	Age ≥75 y	Stroke (<1 mo)
Minor surgery	Arthorscopic surgery	History of VTE	Elective arthroplasty
BMI >25 kg/m	Major open surgery (>45 min)	Family history of VTE	Hip, pelvis or leg fracture
Swollen legs	Laparoscopic surgery (>45 min)	*Factor V Leiden	Acute spinal cord injury (<1 mo)
Varicose veins	Malignancy	*Prothrombin20210A	
Pregnancy or Postpartum	Confined to bed (>72 h)	Lupus anticoagulant	
History of unexpected or reccurrent spontaneous abortion	Immobilizing plaster cast	Anticardiolipin antibodies	
Oral contraceptives or hormone replacement	Central venous access	Elevated serum homocysteine	
Sepsis (<1 mo)		Heparin-induced thrombocytopenia	
Serious lung disease including pneumonia (<1 mo)		Other congenital or acquired thrombophilia	
Abnormal pulmonary function			
Acute myocardiac infarction			
Congestive heart failure (<1 mo)			
History of inflammatory bowel disease			
Medical patient at bed rest			
		Total Risk Factor Score	

*Factor V Leiden and Prothrombin20210A genetic mutation were not measured inthis study, since neither has been seen in Japanese people.

Caprini score (=Total Risk Factor Score)	VTE Risk Level (Patient Undergoing General and Abdominal Surgery)
0	Very low
1～2	Low
3～4	Moderate
≥5	High

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.

the mortality rate remained high (12.9%)[11], and the incidence rate of PTE in 2011 was 0.0063% for the general population, compared to 0.030% for perioperative patients[11], showing an approximately five-fold increase. This means that surgical intervention represents one of the major factors contributing to VTE. Appropriate pre-operative risk assessments and thorough preventive measures are therefore urgently needed.

D-dimer, the degradation product of stabilized fibrin, is widely used for VTE screening in clinical pretests. Caprini score (Table 1) is a point-scoring risk assessment model to predict VTE, dividing individuals into four risk groups based on the total score[10)12)~15)]. The present study reviewed the significance of D-dimer testing for VTE screening and risk assessment by comparing D-dimer levels and Caprini scores.

Materials and Methods

This study involved the 307 patients for whom pre-operative D-dimer level was measured before surgery among the 441 consecutive patients who underwent general or abdominal surgery in the Department of Surgery II at Tokyo Women's Medical University Hospital between July 2012 and June 2013. All study protocols were approved by the institutional review board and informed consent was obtained from all patients prior to participation.

Pre-operative D-dimer levels were determined using the latex agglutination method (Coapresta 2000; Sekisui Medical, Tokyo, Japan and RIAS AUTO D-dimer NEO reagent; Sysmex, Kobe, Japan) in these 307 patients. Participants were then divided into two groups: "high D-dimer group", with D-dimer >1 μg/mL; and "low D-dimer group", D-dimer ≤1 μg/mL. Venous duplex scanning (VDS)

Table 2 Patients' background characteristics

	Number of patients (%)
Age (years)	60.7 ± 16.3 (19-92)*
Sex	
Male	196 (63.8)
Female	111 (36.2)
Disease	
Colorectal cancer	91 (29.6)
Gastric cancer	44 (14.3)
Liver metastasis	8 (2.6)
Pancreas cancer	5 (1.6)
Anal canal cancer	2 (0.7)
Malignant lymphoma	2 (0.7)
Jejunal cancer	1 (0.3)
Inguinal hernia	50 (16.3)
IBD**	27 (8.8)
Cholelithiasis	18 (5.9)
Ileus	17 (5.5)
Appendicitis	11 (3.3)
Cicatricial hernia	9 (2.9)
ITP***	5 (1.6)
Others	17 (5.5)
Operation	
Laparotomy	155 (50.5)
Laparoscopic surgery	95 (30.9)
Percutaneous surgery	50 (16.3)
Transanal surgery	7 (2.3)
D-dimer	
low	204 (66.4)
high	103 (33.6)
Caprini Score	
very low	0
low	25 (8.1)
moderate	91 (29.6)
high	191 (62.2)

*mean ± SD (min-max).
**Inflammatory bowel disease.
***Idiopathic thrombocytopenic purpura.

(LOGIQ 7 PRO; GE Healthcare, Tokyo, Japan) with a 2.5-8.0 MHz transducer using the compression method and enhanced computed tomography (CT) (TSX 101 A / HA (Aquilion 64) or TSX 301 A / 2 A (AquilionONE) ; Toshiba Medical Systems, Tochigi, Japan) were performed for patients in the high D-dimer group and patients with a past or family history of VTE to screen for pre-operative VTE. In addition, the Caprini score, a risk assessment system used in the ACCP guideline[10], was measured in all cases to assess the risk of perioperative VTE, and patients were classified accordingly (0, very low-risk group; 1-2, low-risk group; 3-4, moderate-risk group; ≥5, high-risk group). Based on these results, the following 4 areas were analyzed to clarify the significance of D-dimer testing in screening and risk assessment for VTE:

1) VTE frequency in the high D-dimer group

2) Presence of VTE and correlations to Caprini score

3) Relationship between high / low D-dimer groups and clinicopathological factors of thrombosis Clinicopathological factors examined in relation to thrombosis were: age ≥75 years; past history of thrombosis; family history of thrombosis; positive results for lupus anticoagulant; elevated levels of anticardiolipin antibody; elevated levels of serum homocysteine; malignancy; central venous access; bed rest ≥72 h; body mass index >25 kg/m^2; swelling of the legs; varicose veins; abnormal pulmonary function; congestive heart failure; inflammatory bowel disease; and sepsis (<1 month).

4) Relationship between high / low D-dimer groups and Caprini score or risk group

Statistical analysis was performed using the t-test and the χ^2 test with JMP version 11 software (SAS Institute, Tokyo, Japan). Values of $p<0.05$ were considered significant.

Results

Table 2 shows the characteristics of study participants. Mean (± standard deviation) age at the time of the study was 60.7 ± 16.3 years, with 196 male patients and 111 female patients. There were 154 benign cases (50.2%; inguinal hernia, n = 50; inflammatory bowel disease, n = 27; cholelithiasis, n = 18; ileus, n = 17; appendicitis, n = 11; cicatricial hernia, n = 9; idiopathic thrombocytopenic purpura (ITP), n = 5; and others, n = 17) and 153 malignant cases (49.8%; colorectal cancer, n = 91; gastric cancer, n = 44; liver metastasis, n = 8; pancreatic cancer, n = 5; anal canal cancer, n = 2; malignant lymphoma, n = 2; and jejunal cancer, n = 1). The approach methods were laparoscopic surgery in 95 cases, laparotomy in 155, percutaneous surgery in 50, and transanal surgery in 7. Mean D-dimer level was 0.73 μg/mL (range, 0.2-31.4 μg/mL). As a result, the high D-dimer group included 103 patients (34%) and the low D-dimer group had 204 patients (66%). Mean Caprini score was 5 (range, 1-12). There were 191 (62%) high-risk patients with a Caprini score > 5, 91 (30%)

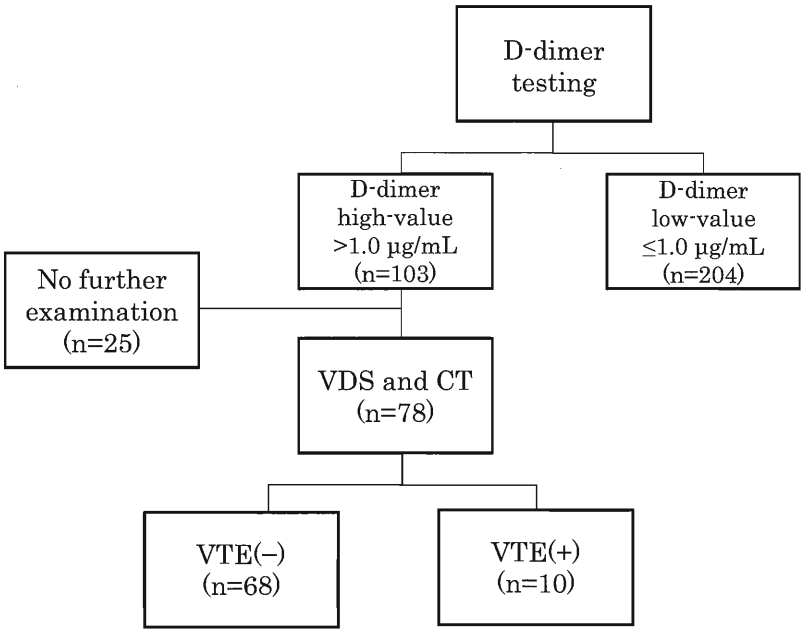

Fig. 1 Pre-operative VTE prevalence in the D-dimer high-value group

moderate-risk patients with a Caprini score of 3-4, 25 (8%) low-risk patients with a Caprini score of 1-2 and no very low-risk patients. In this study, active malignant disease was the most common risk factor for VTE (153 patients, 49.8%), followed by age ≥75 years (67 patients, 21.8%), obesity (44 patients, 14.3%), inflammatory bowel disease (40 patients, 13.0%), past history of thrombosis (10 patients, 3.3%), central venous access (9 patients, 2.9%) and serious lung disease (9 patients, 2.9%). Of the 307 patients referred, VTE was detected pre-operatively in 12 (3.9%).

1. VTE frequency in the high D-dimer group (Fig. 1)

VDS and contrast-enhanced CT were performed for 78 of the 103 patients in the high D-dimer group. VDS was not conducted in the remaining 25 patients (20 patients due to lack of time before surgery, and 5 patients refused). VTE was detected in 10 of the 78 patients (12.8%) who underwent VDS and enhanced CT. VTE was diagnosed by VDS in 9 cases and by enhanced CT in 1 case. Of the 10 cases, 1 case showed symptomatic VTE, while the other 9 involved asymptomatic VTE. Furthermore, 2 of the 10 cases showed proximal DVT with blood clots in the inferior vena cava or femoral vein, while the remaining 8 cases showed distal DVT with blood clots in the peripheral soleus muscle vein or sural vein.

2. Presence of VTE and relationship to Caprini score (Fig. 2)

There were 82 patients in the high D-dimer group or with a past/family history of VTE. Among these, VTE was detected in 12 (14.6%; 10 in the high D-dimer group; 2 with a past/family history of VTE). Mean Caprini score was 6.83 ± 2.04 for VTE-positive cases and 5.54 ± 1.75 for VTE-negative cases. Caprini score was significantly higher in VTE-positive cases than in VTE-negative cases ($p = 0.0238$).

3. Relationship between high / low D-dimer groups and clinicopathological factors of thrombosis

The frequencies of clinicopathological factors associated with thrombosis were compared between high and low D-dimer groups (Table 3). Univariate analysis was performed using the χ^2 test to clarify the relationship between high/low D-dimer groups and the clinicopathological factors of thrombosis. Patients ≥75 years old accounted for 32.0% (33 of 103 cases) of the high D-dimer group and 16.7% (34 of 204 cases) of the low D-dimer group; significantly more patients in the high D-dimer group were ≥75 years old ($p = 0.0021$). Central venous access inser-

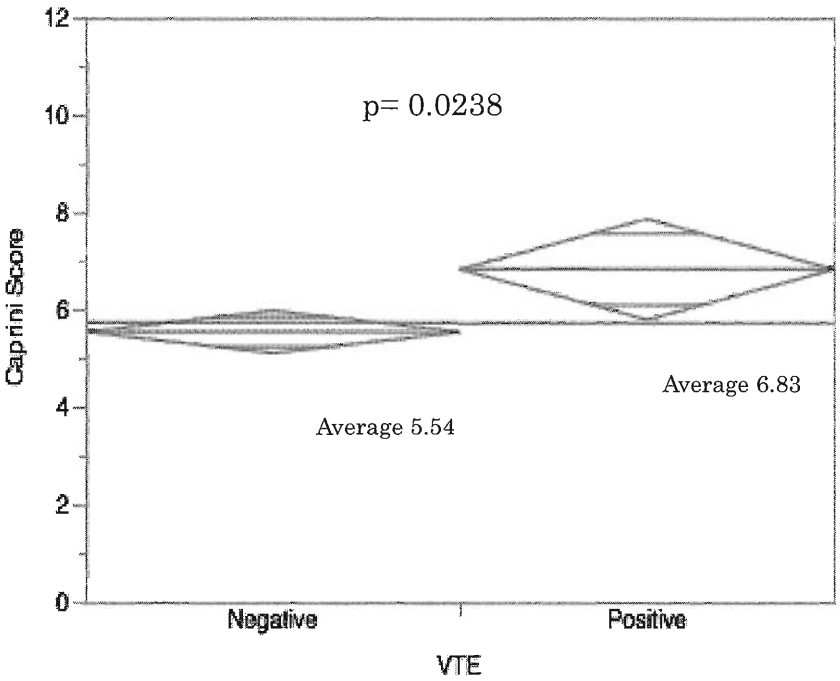

Fig. 2 Relationship between Presence of VTE and Caprini score
In VTE-positive cases, the average Caprini score was 6.83 (±2.04).
In VTE-negative cases, the average Caprini score was 5.54 (±1.75).
The Caprini score was significantly higher in the VTE-positive cases (p=0.0238).

Table 3 Frequency of each clinicopathological factor of thrombosis in the high- and low-value D-dimer groups

	High value of D-dimer (n=103)	Low value of D-dimer (n=204)	p
Age >75 years	33 (32%)	34 (16.7%)	0.0021
Past history of thrombosis	5 (4.9%)	5 (2.6%)	0.2627
Family history of thrombosis	1 (1.0%)	0	—
Positive lupus anticoagulant	0	0	—
Elevated anticardiolipin antibodies	2 (1.9%)	1 (0.5%)	0.2222
Elevated serum homocysteine	0	2 (1.0%)	0.3134
Malignancy (present or previous)	56 (54.4%)	103 (50.5%)	0.5207
Central venous access	6 (5.8%)	3 (1.5%)	0.0327
Bed rest	0	3 (1.5%)	—
Obesity (BMI >25 kg/m^2)	14 (13.6%)	30 (14.7%)	0.7926
Swollen legs/varicose veins	5 (4.9%)	0	—
IBD*	15 (14.6%)	25 (12.3%)	0.5705
Severe lung disease	5 (4.9%)	4 (2.0%)	0.1559
Heart failure	2 (1.9%)	0	—
Sepsis	1 (1.0%)	0	—
Hormone replacement therapy	0	1 (0.5%)	—

*Inflammatory bowel disease.
There are significantly more cases with a high value of D-dimer in cases with age ≥75 years and CV access.

tion was performed in 5.8% (6 of 103 cases) of cases in the high D-dimer group, significantly more than in the low D-dimer group (1.5%, 3 of 204 cases; p=0.0327). Swollen legs and varicose veins were seen in 4.9% (5 of 103 cases) of cases in the high D-dimer group, compared to none in the low D-dimer group. D-dimer level appeared to correlate with age (≥75 years), CV insertion, and the presence of swollen legs and varicose veins.

4. Relationship between high / low D-dimer groups and Caprini score or risk group (Fig. 3)

Mean Caprini score was 5.53±1.86 in the high D-dimer group and 4.74±1.90 in the low D-dimer group. Using the t-test, Caprini score was signifi-

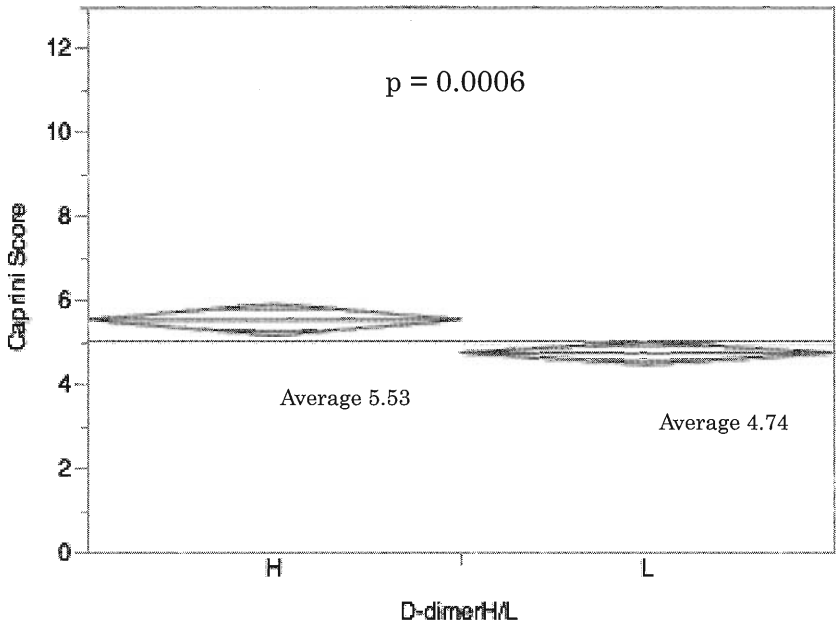

Fig. 3 Relationship between D-dimer high/low groups and Caprini score
In the D-dimer high-value group, the average Caprini score was 5.54 (± 1.86).
In the D-dimer low-value group, the average Caprini score was 4.74 (± 1.90).
The Caprini score was significantly higher in the D-dimer high-value group (p = 0.0006).

cantly higher in the high D-dimer group (p = 0.0006). The four levels of risk factor were regrouped into two groups (very low/low vs. moderate/high) regarding whether pharmacological prophylaxis would be preferred.

Next, we reconstructed 2 × 2 tables. The very low/low risk group comprised 25 cases, while the moderate/high risk group included 282 cases. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated as 0.35 (100/282), 0.88 (22/25), 0.97 (100/103), and 0.11 (22/204), respectively. Positive predictive value was definitely high, indicating that patients with high levels of D-dimer can be expected to show an increase in the risk of VTE to more than moderate.

Discussion

This observational study involved 307 consecutive patients who underwent general surgery at our department over a 1-year period. The Caprini score, validated for VTE risk assessment and listed in the ACCP guideline, was used in this study, and the relationship with D-dimer levels, which are widely used for VTE screening, was analyzed. This study showed that Caprini score was significantly higher for the high D-dimer group, raising the possibility that D-dimer testing might be useful not only to screen for pre-operative VTE, but also to assess the risk of VTE.

VTE was detected in 12 of the 307 patients (3.9%) during pre-operative screening. This was in line with the 3.7-18.4% incidence rate from pre-operative screening in abdominal surgery cases in Japan [15)16)]. The 12 patients showing VTE pre-operatively were treated with fondaparinux, factor Xa inhibitor, and warfarin. Those patients who had been treated with anticoagulant due to co-morbidity were heparinized. All other patients received mechanical prophylaxis (elastic stockings (ES) and/or intermittent pneumatic compression (IPC)) or pharmacological prophylaxis (enoxaparin, low molecular weight heparin (LMWH)) based on the Caprini score while considering the risk of bleeding complications. No patients developed symptomatic PTE within 1 year postoperatively.

D-dimer is a degradation product of stabilized fibrin, one of the many fibrin/fibrinogen degradation products, and is only applicable for secondary fibrinolysis. The molecule is widely used for excluding a diagnosis of VTE due to its convenience and high sensitivity [17)~21)]. In Japan, D-dimer testing for VTE is

not yet covered by the national health insurance system. However, the efficiency of D-dimer testing in screening for VTE has been mentioned in the Guidelines for the Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis published by the Japanese Circulation Society[2]. On the other hand, limits exist to the degree to which D-dimer testing can be used alone for diagnosing VTE[22)23)]. The positive predictive value is low, because results may be affected by other pathological conditions that may produce fibrin thrombus, such as inflammation, infection, trauma, tumor, postoperative status, myocardial infarction, and cerebrovascular disease. Moreover, standard values vary with the methodology of D-dimer measurement and the device used, with values of 500 μg/L used in many Western countries and 1-1.5 μg/mL applied in Japan. Standardization or harmonization has been expected, but has yet to be achieved. In this study, the standard value was established as 1 μg/mL, based on the conventional value for the measurement device. D-dimer level is also affected by age, so age-adjusted D-dimer cut-off values of 500 μg/L for individuals $<$50 years old and age (in years) $\times$ 10 μg/L for individuals over 50 years old were applied[24)25)]. A meta-analysis revealed that this cut-off increases specificity without modifying sensitivity, thereby improving the clinical utility of D-dimer testing[26)]. This approach also appears worth applying in Japan.

VDS was used instead of angiography for noninvasive testing, and its effectiveness for DVT diagnosis in the femoral vein close to the peripheral veins has been confirmed[27)28)]. However, preoperative scanning of all cases is difficult, because VDS requires expert skills and time for testing. Enhanced CT is effective for diagnosing DVT and PTE in the popliteal vein close to the central vein, but issues remain in VTE diagnosis using VDS and enhanced CT, such as contrast media allergy and renal dysfunction, as well as difficulties in general application. Since VDS and enhanced CT were not conducted in the low D-dimer group in the present study, we cannot be certain that asymptomatic VTE was not overlooked, but at least no postoperative cases of symptomatic VTE were detected. As such, highly efficient VTE screening[10)] may be possible by looking at the D-dimer level in association with VDS and enhanced CT data. In addition, studies have been conducted on improving diagnostic accuracy, such as setting cut-off levels for D-dimer[20)21)29)~31)], combining D-dimer level with pretest clinical probability score, setting the cut-off level by the number of days after operation[32)], and standardization or harmonization of D-dimer levels[32)33)]. Future clinical applications are therefore expected.

The Caprini score is a point-scoring risk assessment model advocated by Caprini to predict VTE. This score has been used in medical and surgical patients since the late 1980s and modified versions were published in 2005 and 2010[13)14)]. This score has proven effective and is widely used even outside of the United States[34)35)], with translation of the tool into 12 languages and recognition as an extremely useful risk-assessment model. In Japan, this score is not mentioned in the guideline and the score is not common. The most recent version is presented in Figure 1. Approximately 40 risk factors are listed, with weights of 1-5 points each according to relative risk. For instance, stroke and spinal cord injury counts as 5 points, because incidence rates of PTE have been reported as an extremely high 6% in stroke patients and 5% in spinal injury patients[1)]. Factor V Leiden and prothrombin G20210A genetic mutations were not measured, since neither has been seen in Japanese individuals[36)]. Total risk factor score was then originally used to categorize patients into 1 of 4 risk groups (low, moderate, high, and highest). The score has been validated and modified for specific use. For general and abdominal surgery patients, VTE risk is categorized as very low (0 points), low (1-2 points), moderate (3-4 points), and high ($\geq$5 points) and preventive measures are recommended according to risk in the 9th ACCP guideline. The present study used the latter 4 risk groups. Early ambulation alone is recommended for the very low risk group, mechanical prophylaxis such as IPC for the low risk group, mechanical or pharmacological prophylaxis such as low-dose unfractionated heparin or LMWH, and mechanical

(IPC or ES) and pharmacological prophylaxis for the high risk group.

However, since the point system is cumbersome and there are several special blood test requirements, such as lupus anticoagulant, homocysteine, and anti-cardiolipin antibody, there is strong demand for a risk assessment system that can be more easily used extensively. The present results showed that patients in the high D-dimer group showed high Caprini scores. In other words, these individuals are in the VTE high-risk group. Any simpler and more convenient VTE risk assessment method established using D-dimer would be used in place of Caprini score.

This study did not have sufficient power to determine the efficiency of D-dimer for VTE risk assessment, due to the design as a retrospective analysis in a single institution with a limited pool of patients and a lack of postoperative data. Further study (such as a multi-center study with substantial postoperative evaluation) and positive verification of the results of VTE screening and VTE incidence risk assessment using D-dimer testing are thus needed.

Conclusion

This observational study involving 307 consecutive general surgery and abdominal patients seen at our department over a 1-year period suggested that simple D-dimer testing might be worth discussing and considering not only to screen for pre-operative VTE, but also to assess the perioperative VTE risk level.

The authors have no conflicts of interest to declare.

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一般外科/腹部外科手術症例における静脈血栓塞栓症評価のための D-dimer 測定の意義

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本研究では，D-dimer 値と Caprini score との比較から静脈血栓塞栓症（VTE）のスクリーニングおよびリスク評価における術前 D-dimer 測定の意義について検討した．当科における1年間の腹部/一般外科手術症例を対象とした．術前に307例全例に，D-dimer を測定した．D-dimer 高値群（>1 μg/mL）あるいは VTE の既往/家族歴を有する82例に対し，下肢静脈エコーおよび造影 CT を行った．12例に VTE を認めた．VTE の頻度は全症例中3.9% であった．Caprini score を測定し，VTE のリスク評価を行った．Caprini score の平均値は，VTE 陽性例では 6.83（±2.04），陰性例では 5.54（±1.75）であり，p＝0.0238 と VTE 陽性例では Caprini score が有意に高く，Caprini score は VTE のリスク評価に有用であると考えた．また，Caprini score の平均値は D-dimer 高値群では 5.53（±1.86），低値群では 4.74（±1.90）であり，p＝0.0006 と D-dimer 高値群では Caprini score が有意に高かった．D-dimer 高値群では Caprini Score が有意に高く，D-dimer 値が VTE のスクリーニングのみならず，VTE 発症のリスク評価においても有用である可能性が考えられた．