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CLINICAL ARTICLE

Sequential screening to predict symptomatic pulmonary thromboembolism after gynecologic surgery in Nara, Japan

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ABSTRACT

Objective: To evaluate a sequential screening method's efficacy in predicting symptomatic pulmonary thromboembolism (PTE) after gynecologic surgery. *Methods:* A prospective study employing a two-stage screening process was conducted among consecutive asymptomatic adults who underwent outpatient evaluation for gynecologic surgery at Nara Medical University Hospital, Japan, between April 1, 2004, and December 31, 2013. Patients with a preoperative plasma D-dimer level greater than or equal to 1.0 μg/mL underwent compression ultrasonography of the lower extremities. The primary outcome measure was postoperative detection of symptomatic PTE. *Results:* Overall, 1729 patients were included. The mean D-dimer level was 1.7 ± 3.3 μg/mL. Compression ultrasonography was conducted among 470 (27.1%) patients with positive D-dimer test results; symptomatic deep vein thrombosis (DVT) was preoperatively detected among 94 (20.0%) of them. Patients with DVT (n = 94) had higher D-dimer levels than patients (n = 1635) without (7.8 ± 12.8 μg/mL vs 1.1 ± 1.8 μg/mL; $P < 0.001$). Despite anticoagulant therapy, symptomatic PTE was detected postoperatively among two of these 94 patients. Symptomatic PTE was also detected among four of 376 patients with positive D-dimer test results but no evidence of DVT by ultrasonography. No clinical onset of postoperative PTE was observed among 1259 patients with D-dimer levels below the cut-off value. *Conclusion:* The PROVEN screening strategy (Preoperative surveillance using a sequential strategy) was ineffective at predicting postoperative symptomatic PTE.

1. Introduction

Venous thromboembolism (VTE)—which includes deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE)—is a serious complication associated with gynecologic surgery [1]. The rate of VTE among women undergoing such surgery is high, particularly among those with a gynecologic malignancy, and the overall risk of DVT is estimated at 7%–45% [2]. Of note, the prevalence of proximal DVT is approximately 70% among patients with PTE confirmed by angiography [3]. Therefore, women undergoing major gynecologic surgery should be offered thromboprophylaxis [4–6].

Many imaging modalities are used in the diagnostic algorithm for VTE. Compression ultrasonography (or venous ultrasonographic imaging) is a convenient, reproducible, and highly accurate method for the detection of DVT that has replaced venography in clinical practice [7]. Furthermore, the plasma D-dimer test is an established method for early detection of VTE [8,9].

Over the past decade, the Nara Medical University Hospital in Japan has used a sequential strategy involving plasma D-dimer measurement followed by ultrasonography to preoperatively screen for VTE among patients who have undergone gynecologic surgery. This patient-based screening approach is known as the Programme for VTE Screening Study at Nara, Japan (PROVEN).

The aim of the present study was to determine whether PROVEN is useful for predicting preoperative asymptomatic DVT and postoperative symptomatic PTE.

2. Materials and methods

A single-center prospective study was conducted among consecutive asymptomatic adults who underwent outpatient evaluation for gynecologic surgery in the Department of Obstetrics and Gynecology, Nara Medical University Hospital, between April 1, 2004, and December 31, 2013. The inclusion criteria were age older than 20 years and gynecologic surgery for uterine leiomyoma, endometriosis, pelvic organ prolapse, ovarian cyst, cervical cancer, endometrial cancer, or ovarian cancer. The exclusion criteria were pregnancy or lactation; suspected DVT or PTE; ongoing anticoagulation therapy; mandatory indication for anticoagulation therapy; and geographic inaccessibility to follow-up. The participants' medical records were abstracted for relevant

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ultrasonography, computed tomography, and clinical data, including VTE diagnosed either preoperatively or postoperatively. The study was conducted according to the ethical principles stated in the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of Nara Medical University. The purpose and details of PROVEN were explained to the patients; written informed consent was obtained before participation.

The PROVEN screen for PTE was a two-stage process (Fig. 1). Patients with a plasma D-dimer level of 1.0 μg/mL or higher subsequently underwent ultrasonography, whereas those with a D-dimer level of less than 1.0 μg/mL did not receive a referral for ultrasonography. All participants were scheduled for surgery and a 3-month follow-up evaluation. Patients who presented with clinical signs of PTE postoperatively underwent enhanced computed tomography of the lungs to diagnose this condition.

All patients received appropriate thromboprophylaxis according to the Japanese VTE guideline recommendations [10]. This guideline stratifies patients into low, moderate, high, and very high risk groups according to their actual VTE risk and recommends optimum VTE prophylaxis for each group. The guideline also recommends early ambulation for low-risk patients (surgical time <30 minutes). The use of graduated compression stockings or intermittent pneumatic compression is recommended for moderate-risk patients undergoing gynecologic surgery for benign disease. For high-risk patients with malignant disease, intermittent pneumatic compression or pharmacological prophylaxis with low molecular weight heparin (4000 IU/day) or low-dose unfractionated heparin (10 000–15 000 units/day) is recommended. Mechanical and pharmacological prophylaxis are recommended if patients with malignant disease have any additional risk factors, including previous VTE or thrombophilia (very high-risk group).

Patients with VTE were treated according to the Japanese VTE guidelines [10]. Conventional anticoagulant therapy was initiated after the diagnosis of DVT. An inferior vena cava filter was placed in patients with proximal DVT or floating DVT for preoperative prophylaxis of PTE.

Quantitative measurement of plasma D-dimer levels was performed two weeks prior to the date of surgery using the AIA-PACK DD immunoenzymometric assay kit (Tosoh Medics, Foster City, CA, USA). A plasma D-dimer level of less than 1.0 μg/mL was reported to be sufficient to exclude VTE among patients with a negative D-dimer level without needing to perform ultrasonography [11].

The gold standard for DVT diagnosis in the present study was ultrasonography using vein compression. Imaging was performed on the lower extremities with a 5-MHz transducer connected to a Sonovista-SL MEU 1577 ultrasonographic unit (Mochida Pharmaceutical, Tokyo, Japan). Routine scanning methods for compression ultrasonography were previously established to shorten the time required for examination and ensure consistent conditions during secondary screening [12].

The preoperative incidence of DVT among the participants was determined. The primary outcome measure was the number of patients with symptomatic PTE after undergoing gynecologic surgery.

Participants were registered in a computer system to aid data collection and management. The data were analyzed using SPSS version 11.0 (IBM, Armonk, NY, USA). Differences between the observed results were evaluated using the χ^2 test, whereas differences between the means were evaluated by the *t* test and analysis of variance. A *P* value below 0.05 was considered statistically significant.

3. Results

Of the 1729 patients enrolled, 934 (54.0%) had benign disease and 795 (46.0%) had malignant disease (Fig. 1). A total of 470 (27.2%) patients met the preoperative D-dimer cut-off level for ultrasonography, which was scheduled within 1 week. The preoperative ultrasonography data revealed asymptomatic DVT among 94 (20.0%) of the 470 patients with a positive D-dimer test result, giving an overall prevalence of 5.4% (94 of 1729). The incidence of preoperative DVT was 65 of 795 (8.2%) among patients with gynecologic cancer and 29 of 934 (3.1%) among those with benign disease. Proximal DVT was found among 14 (14.9%) of the 94 patients with DVT.

The incidence of confirmed symptomatic PTE during the postoperative follow-up period was six of 1729 (0.4%) for all participants and six of 470 (1.3%) for those with a positive D-dimer test result. The case histories of the six patients with PTE are shown in Table 1.

Two of these patients presented with DVT preoperatively. Patient 1 had a large uterine leiomyoma weighing 1865 g; she exhibited

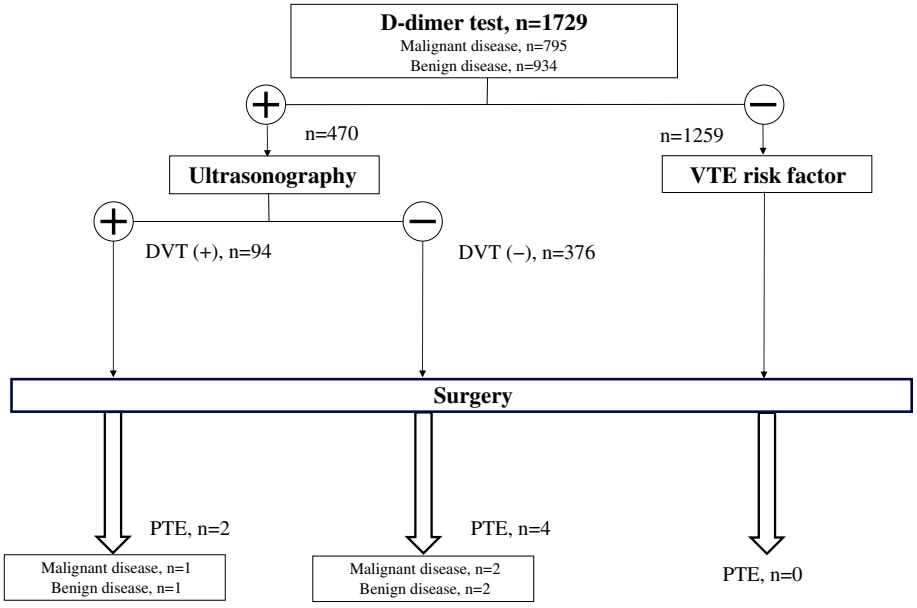

Fig. 1. Flow diagram of the two-point screening strategy for predicting pulmonary thromboembolism after gynecologic surgery. The screening protocol comprised a plasma D-dimer assay followed by compression ultrasonography; the whole-leg strategy comprised whole-leg color-coded Doppler ultrasonography. The plus and negative symbols indicate positive and negative test results, respectively. Abbreviations: VTE, venous thromboembolism; DVT, deep vein thrombosis; PTE, pulmonary thromboembolism.

Table 1
Case histories of the six patients with postoperative PTE.[a,b]

Patient	Age, y	Disease	BMI	Complication	Preoperative D-dimer level, μg/mL	Preoperative DVT	Type of PTE	Postoperative timing of PTE onset
1	37	Leiomyoma	30.4	History of DVT	1.4	Yes	Non-massive	Day 15
2	61	Cervical cancer, stage IIB	27.1	Thrombophilia; protein C deficiency	7.6	Yes	Non-massive	Day 5
3	74	Uterine prolapse	28.8	Atrial fibrillation; hypertension	1.4	No	Non-massive	Day 1
4	56	Leiomyoma	23.0	None	2.7	No	Non-massive	Day 2
5	64	Endometrial cancer, stage Ic	30.4	Hypertension	1.4	No	Non-massive	Day 2
6	83	Endometrial cancer, stage IIa	28.8	None	3.4	No	Massive	Day 26

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); DVT, deep vein thrombosis; PTE, pulmonary thromboembolism.
[a] The diagnostic method was lung perfusion scintigraphy plus enhanced chest computed tomography for all cases, with the exception of patient 6, who underwent enhanced chest computed tomography only.
[b] All patients recovered.

asymptomatic unilateral DVT of the left leg. Patient 2 had stage IIb cervical cancer and bilateral asymptomatic DVT. For both patients, inferior vena cava filter placement was used owing to DVT in proximal veins or floating DVT. Postoperative laboratory analysis indicated that patient 2 had either thrombophilia or exhibited a prothrombotic state owing to reduced protein C levels in the circulation and activated protein C resistance. Activated protein C resistance is a hemostatic disorder characterized by a poor anticoagulant response to activated protein C. This results in an increased risk of venous thrombosis. For both patients, conventional anticoagulant therapy with low-dose unfractionated heparin was started immediately after surgery, as were prophylactic measures, including the use of graduated compression stockings. The onset of PTE was hypothesized to reflect recurrent DVT, which had developed during postoperative immobilization.

As shown in Fig. 1, preoperative DVT was excluded by ultrasonography among 376 of the 470 patients with a positive D-dimer test result (0.8%). Nevertheless, four of these 376 patients developed symptomatic PTE postoperatively (Table 1) and, based on Japanese VTE guidelines, which recommend that patients without preoperative DVT receive intermittent pneumatic compression intraoperatively and postoperatively, received graduated compression stockings plus intermittent pneumatic compression postoperatively for 2–3 days.

None of the 1259 patients with a plasma D-dimer level less than 1.0 μg/mL developed symptomatic PTE within 3 months of undergoing surgery (Fig. 1). These patients had a 0.0% probability of developing symptomatic PTE postoperatively, whereas the probability increased to 1.3% among those with a positive D-dimer test result.

Table 2 shows the patient characteristics with respect to plasma D-dimer levels, which were in the range of 0.0–90.1 μg/mL for the cohort as a whole. The mean D-dimer level was substantially elevated among the 246 patients with ovarian cancer (4.0 ± 6.4 μg/mL). The level was also higher among patients with malignant tumors (n = 795; 2.1 ± 5.4 μg/mL) than those with benign disease (n = 934; 0.9 ± 1.3 μg/mL; $P < 0.001$). Patients with DVT (n = 94) had higher D-dimer levels than the 1635 patients without DVT (7.8 ± 12.8 μg/mL vs 1.1 ± 1.8 μg/mL; $P < 0.001$).

4. Discussion

In the present study, postoperative symptomatic PTE was detected among six patients, four of whom had negative preoperative ultrasonography screening results for DVT. These results suggested that preoperative surveillance using the sequential screening strategy was not useful for early symptomatic detection of PTE after gynecologic surgery.

Postoperative prevention of PTE has become widespread [4–6]; however, the optimum method to detect DVT before surgery and the type of prophylactic treatment that should be offered to women who screen positive for this condition remain unclear. The PROVEN screening strategy was a two-stage sequential process, in which only those patients with a preoperative plasma D-dimer level of 1.0 μg/mL or greater were referred for ultrasonography. Asymptomatic DVT was preoperatively diagnosed in 5.4% of screened participants; symptomatic PTE developed within 1 month after surgery in 0.4%. The potential complications were not fully appreciated among two of the six patients with PTE despite use of anticoagulant therapy both preoperatively and postoperatively. In addition, DVT could not be detected preoperatively in the remaining four patients. Concomitant malignancy, large pelvic masses, and a history of DVT and thrombophilia were the suspected prevalent factors among the patients with postoperative PTE. The present findings were consistent with previously published data [13].

Silent or subclinical VTE frequently occurs before surgery for gynecologic cancers, including ovarian cancer [14] and endometrial cancer [15]. Ultrasonographic studies show that the incidences of DVT among patients with and without gynecologic cancer are 4.2% and 0.2%, respectively [13]. Meanwhile, the incidence of PTE among hospitalized

Table 2
Association of plasma D-dimer levels with patient characteristics.[a,b]

Disease type	Total cohort		DVT detected		DVT not detected		*P* value
	No. of patients	Plasma D-dimer level, μg/mL[b]	No. of patients	Plasma D-dimer level, μg/mL[b]	No. of patients	Plasma D-dimer level, μg/mL[b]	
Malignant	795	2.1 ± 5.4 (0.0–90.1)	65	9.3 ± 14.9 (1.1–90.1)	730	1.5 ± 2.2 (0.0–16.4)	<0.001
Ovarian cancer	246	4.0 ± 6.4 (0.1–56.6)	38	10.8 ± 12.4 (1.2–56.6)	208	2.8 ± 3.3 (0.0–16.4)	<0.001
Uterine cervical cancer	270	0.8 ± 0.9 (0.0–6.1)	6	2.6 ± 1.5 (1.1–4.9)	264	0.7 ± 0.8 (0.0–6.1)	0.012
Uterine endometrial cancer	263	1.7 ± 6.1 (0.1–90.1)	19	8.1 ± 20.3 (1.1–90.1)	244	1.1 ± 1.5 (0.1–12.0)	<0.001
Other	16	7.6 ± 11.7 (0.7–21.1)	2	1.8 ± 1.9 (1.1–2.2)	14	1.3 ± 0.4 (0.1–3.2)	0.424
Benign	934	0.9 ± 1.3 (0.0–13.4)	29	4.4 ± 3.1 (1.3–13.4)	905	0.8 ± 1.0 (0.0–11.2)	<0.001
Ovarian tumor	401	0.9 ± 1.4 (0.0–10.7)	9	4.2 ± 1.6 (2.0–6.2)	392	0.9 ± 1.3 (0.0–10.7)	<0.001
Leiomyoma and/or adenomyosis	407	0.9 ± 1.4 (0.0–13.4)	17	4.7 ± 3.8 (1.3–13.4)	390	0.7 ± 0.8 (0.0–11.2)	<0.001
Other	126	0.7 ± 0.7 (0.1–3.8)	3	2.5 ± 0.1 (2.4–2.5)	123	0.6 ± 0.1 (0.1–3.8)	<0.001
Total	1729	1.7 ± 3.3 (0.0–90.1)	94	7.8 ± 12.8 (1.1–90.1)	1635	1.1 ± 1.8 (0.0–16.4)	<0.001

Abbreviation: DVT, deep vein thrombosis.
[a] Values given as number or mean ± standard deviation (range).
[b] Measured using immunoenzymometric assay kit.

patients in Japan is 0.03% [16]. The increased incidence of postoperative PTE recorded in the present study (0.4%) suggested that it might be necessary to establish a more efficient diagnostic and prophylactic system for VTE [17].

Primary care physicians require simple methods to rule out VTE. The D-dimer assay used in the present study is considered to exhibit high reproducibility and high negative predictive value. Several meta-analyses have assessed the use of this assay in the exclusion of VTE [18,19]. Accordingly, the present study found that a negative D-dimer test result could be used to exclude symptomatic PTE postoperatively. The major benefits of using this test are diminished burden on diagnostic resources (the test is simple and widely available) and convenience for both patients and doctors (only a blood sample is required). Although high D-dimer levels are associated with the presence of VTE, the main disadvantage of the test is insufficient sensitivity. The PROVEN study showed that the sensitivity of measuring plasma D-dimer level alone was only 20.0% for predicting DVT preoperatively and 1.3% for predicting the development of PTE postoperatively, thus limiting the usefulness of this assay for early VTE detection. Additional studies are required to explain the wide range of preoperative D-dimer levels recorded in the present study among patients with gynecologic tumors who develop PTE postoperatively.

Despite intensive anticoagulant therapy, two of the patients in the present study who exhibited high plasma D-dimer levels and were diagnosed with DVT by ultrasonography developed PTE postoperatively. For such patients, it is important to recognize that DVT tends to be recurrent and might subsequently develop into PTE. Knowledge of the features of the initial event (proximal DVT) and any associated factors (surgery, malignancy, large pelvic mass, and thrombophilia) on a per patient basis are essential in estimating the risk of recurrence after discontinuation of anticoagulant treatment [20,21]. The results of the present study were consistent with those in the literature [20,21]. Therefore, objectively diagnosed DVT, even if asymptomatic, might require full and prolonged anticoagulation treatment among patients with high-risk factors [20,21]. Serial testing could help to clarify this issue.

A negative ultrasonography result might be unreliable in the presence of a high D-dimer level given that 1.1% of such patients in the present study developed PTE postoperatively. Thus, the findings demonstrate that current strategies are insufficient for predicting the development of symptomatic PTE postoperatively. An elevated D-dimer level following cessation of anticoagulation therapy is associated with an increased risk of recurrent thrombosis [22]. The present findings suggested that patients with positive preoperative D-dimer test results should be treated with anticoagulants irrespective of whether they have positive ultrasonography results.

The diagnosis of VTE requires not only objective tests (D-dimer assay and ultrasonographic detection) but also clinical probability assessment. Clinical items, such as simple clinical decision rules, are important for predicting and/or ruling out VTE. The well-established pretest clinical probability model of Wells et al. [23] can classify patients as having a low, moderate, or high probability of DVT with reasonable accuracy. Independent risk factors for the presence of DVT include previously documented DVT, the presence of active untreated cancer, surgery within the previous 1 month, vein distension, difference in calf circumference, immobilization of the lower extremities, and oral contraceptive use [24]. Indeed, in the present study, postoperative PTE was associated with large pelvic masses, malignancy, and thrombophilias, such as protein C deficiency. Clinical assessment and objective testing have the additional advantages of enabling the management of patients with asymptomatic DVT and prediction of the development of PTE when ultrasonographic or radiographic imaging approaches are not routinely available.

In conclusion, high levels of D-dimer were associated with the presence of preoperative asymptomatic DVT among patients with gynecologic disease. In addition, postoperative symptomatic PTE could be safely excluded on the basis of a single negative D-dimer test result. Nevertheless, a preoperative D-dimer test followed by ultrasonography was not a reliable diagnostic strategy for the management and prediction of symptomatic PTE postoperatively. Therefore, additional studies are required to determine factors affecting the development and recurrence of VTE, as well as the duration of anticoagulation treatment.

Conflict of interest

The authors have no conflicts of interest.

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