Original Article - Urological Oncology

Investig Clin Urol 2021;62:166-171.
https://doi.org/10.4111/icu.20200300
pISSN 2466-0493 • eISSN 2466-054X

INVESTIGATIVE AND CLINICAL UROLOGY
ICUROLOGY

Significance of preoperative screening of deep vein thrombosis and its indications for patients undergoing urological surgery

Shuichi Tatarano, Hideki Enokida, Masaya Yonemori, Rumiko Eura, Hirofumi Yoshino, Hiroaki Nishimura, Yasutoshi Yamada, Masayuki Nakagawa

Department of Urology, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan

Purpose: Preoperative deep vein thrombosis (pre-DVT) is a risk of symptomatic venous thromboembolism (VTE) and a serious postoperative surgical complication. However, little is known about pre-DVT in patients undergoing surgery. This study aimed to investigate the incidence and screening criteria of pre-DVT in patients undergoing urological surgery.

Materials and Methods: Between 2015 and 2017, 320 patients admitted to our hospital for urological surgery were included in this retrospective study. All patients underwent preoperative D-dimer testing. Patients with elevated D-dimer (≥1.0 μg/mL) levels underwent lower-limb compression ultrasonography (CUS). Clinical parameters were analyzed as predictors of pre-DVT, and modest cutoff value of D-dimer to predict pre-DVT were evaluated.

Results: Of 320 patients, preoperative elevated D-dimer levels and DVT were found in 81 (25.3%) and 20 (6.3%) patients, respectively. The positive predictive value (PPV) was 24.7% (20/81). ROC curve analysis revealed a cutoff D-dimer level of 1.8 μg/mL, yielding a PPV of 40.7% for pre-DVT among patients with elevated D-dimer levels. Preoperative DVT was detected in 16 (7.6%, n=210) patients with malignancy, 3 (5.7%, n=53) with adrenal tumors, and in 1 (1.8%, n=57) kidney donor. An age of >70 years was significantly associated with risk for pre-DVT (odds ratio, 2.81; 95% confidence interval, 1.12–7.19; p=0.0270). During a postoperative follow-up period of 90 days, no patient developed symptomatic VTE.

Conclusions: The incidence of pre-DVT was 6.3% in patients undergoing urological surgery. Elderly patients and/or a cutoff D-dimer level of 1.8 μg/mL might be good indications for pre-DVT screening by CUS.

Keywords: Compression ultrasonography; Fibrin fragment D; Preoperative deep vein thrombosis; Urologic surgery; Venous thrombosis

INTRODUCTION

Venous thromboembolism (VTE) including pulmonary thromboembolism (PTE) can be a fatal complication after surgery. Previous studies have reported that postoperative VTE occur in 0.76%–1.0% and 0.42%–0.7%, respectively, in the analyses of large number of patients after undergoing urological surgery [1,2]. However, currently little is known about the correlation between 'preoperative' deep vein thrombosis (pre-DVT) and symptomatic VTE after surgery. Also, few

Received: 28 June, 2020 • **Revised:** 25 September, 2020 • **Accepted:** 18 November, 2020 • **Published online:** 24 February, 2021
Corresponding Author: Hideki Enokida https://orcid.org/0000-0002-3050-9700
Department of Urology, Graduate School of Medical and Dental Sciences, Kagoshima University, 8-35-1 Sakuragaoka, Kagoshima 890-8520, Japan
TEL: +81-99-275-5395, FAX: +81-99-275-6637, E-mail: henokida@m2.kufm.kagoshima-u.ac.jp

studies have reported on pre-DVT in patients undergoing urological surgery. Generally, pre-DVT should be considered an indication for anticoagulant treatment before surgery and a contraindication for use of an intermittent pneumatic compression device (IPC), which may cause life-threatening PTE [3]. Therefore, screening for pre-DVT might be useful for the prevention of postoperative VTE including PTE.

The plasma D-dimer test is frequently used because it is easy to perform. However, its low specificity for detecting pre-DVT requires additional diagnostic evaluations such as lower-limb venous compression ultrasonography (CUS). Therefore, other criteria might be needed for accurate identification of pre-DVT. This study aimed to investigate the incidence of pre-DVT in patients about to undergo urological surgery and to evaluate the utility of D-dimer testing and CUS as screening methods for pre-DVT.

MATERIALS AND METHODS

1. Statement of ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or national research committee and with the 2013 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol and informed consent documents were reviewed and approved by the Institutional Review Boards of the Kagoshima University Hospital (approval number: 190216).

2. Study design

A total of 320 patients who were admitted to Kagoshima University Hospital for urological surgery between May 2015 and December 2017 were considered eligible for this retrospective study. D-dimer testing has been routinely applied to all patients at our hospital.

According to the study protocol and in accordance with our institution, every study patient underwent preoperative D-dimer testing. Patients with elevated D-dimer (≥1.0 μg/mL) levels underwent lower-limb CUS (Fig. 1). The following clinical parameters were assessed as possible predictors of pre-DVT: age, sex, body mass index, presence of malignancy, steroid use, and preoperative serum D-dimer level. We also assessed the prevalence of pre-DVT in patients stratified according to whether they were undergoing urological surgery for malignancy or a benign condition. We performed receiver operating characteristic (ROC) curve analysis to determine a modest D-dimer cutoff value for detecting pre-DVT.

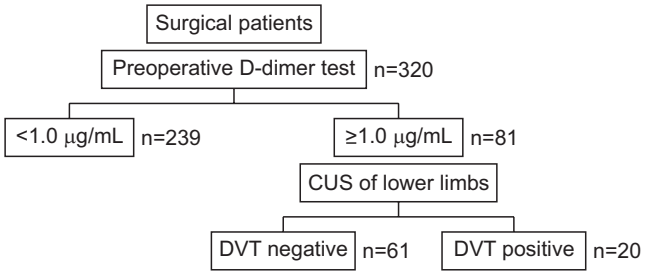

Fig. 1. Study protocol. CUS, compression ultrasonography; DVT, deep vein thrombosis.

The patients underwent laparoscopic surgery (n=240), robotic surgery (n=44), or transurethral surgery (n=36) (Supplementary Table 1). Patients identified with pre-DVT were prescribed direct oral anticoagulant agents (DOAC) such as Edoxaban (30 mg, s.i.d for 3 weeks) or Apixaban (10 mg, b.i.d for 1 week; followed by 5 mg, b.i.d for 2 weeks), and then underwent re-evaluation to confirm remission of DVT by using CUS. In case of insufficient remission of DVT at 3 weeks, duration of DOAC was prolonged by the cardiologists. General anticoagulant prophylaxis for all patients was not used except for the patients with a past history of VTE. Mechanical prophylaxis methods such as use of IPC and compression stockings were employed for each patient. However, IPC was only used for patients who were not identified with pre-DVT.

3. Statistical analysis

The EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is based on R (version 4.0.2; The R Foundation for Statistical Computing, Vienna, Austria) and R commander (version 2.7-0) were employed for statistical analysis in this study [4]. Logistic regression analysis was used for univariate and multivariate analysis for predicting DVT. The optimal cut-off value of the D-dimer level was determined by ROC curve analysis. A p-value <0.05 was considered to indicate statistical significance.

RESULTS

Our study cohort consisted of 210 patients with malignancies and 110 with benign conditions (Table 1). Of 320 patients, preoperative elevated D-dimer levels and DVT were found in 81 (25.3%) and 20 (6.3%) patients, respectively (Fig. 1). Among patients with elevated D-dimer levels, the positive predictive value (PPV) was 24.7% (20/81). The malignancies included kidney cancer, upper tract urothelial cancer (UTUC), prostate cancer, and bladder cancer; and the benign conditions included patients with benign adrenal tumors and kidney donors. Among the 210 patients with malignan-

Table 1. Preoperative DVT prevalence by disease/condition of study patients

Patient disease	Number of patients	Prevalence of DVT	
		Yes	No
Malignant disease	210	16 (7.6)	194
Kidney cancer	67	9 (13.4)	58
UTUC	18	1 (5.6)	17
Bladder cancer	46	4 (8.7)	42
Prostate cancer	79	2 (2.5)	77
Benign disease	110	4 (3.6)	106
Adrenal tumor	53	3 (5.7)	50
Kidney donor	57	1 (1.8)	56
Total	320	20 (6.3)	300

Values are presented as number only or number (%).
DVT, deep vein thrombosis; UTUC, upper urinary tract cancer.

Table 2. Clinical factors according to patients with/without preoperative DVT

Variable	Total (n=320)	DVT	
		Yes (n=20)	No (n=300)
Age (y)		65.8 (40.0–77.5)	67.0 (33.0–71.0)
Body mass index (kg/m^2)		22.9 (15.4–32.2)	23.9 (16.8–30.3)
Sex			
Male	228	11	217
Female	92	9	83
Hypertension			
Yes	183	10	173
No	137	10	127
Diabetes mellitus			
Yes	59	3	56
No	261	17	244
Hyperlipidemia			
Yes	81	7	74
No	239	13	226
Malignancy			
Yes	210	16	194
No	110	4	106
Current tobacco smoker			
Yes	73	2	71
No	247	18	229
Steroid administered			
Yes	7	2	5
No	313	18	295
Anticoagulant administered			
Yes	55	3	52
No	265	17	248

Values are presented as median (interquartile range) or number only.
DVT, deep vein thrombosis.

cies, pre-DVT was detected in 13.4%, 5.6%, 8.7%, and 2.5% of the patients with kidney cancer, UTUC, bladder cancer, and prostate cancer, respectively. The patients' clinical characteristics and the number of patients with pre-DVT are shown in Table 2. Univariate and multivariate analyses of candidate clinical factors for predicting high D-dimer value (≥1.0 μg/mL) are shown in Table 3. Among the significant predictors for high D-dimer value identified by univariate analy-

https://doi.org/10.4111/icu.20200300

Table 3. Univariate and multivariate analyses of clinical factors for D-dimer ≥1.0 μg/dL

Variable	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Age >70 y	3.86	2.28–6.61	<0.0001	2.93	1.64–5.31	0.0003
BMI >30 kg/m^2	0.88	0.20–2.98	0.8548	-	-	-
Male, sex	1.15	0.66–1.99	0.6118	-	-	-
Hypertension	1.53	0.91–2.61	0.1137	-	-	-
Diabetes mellitus	1.29	0.67–2.40	0.4302	-	-	-
Hyperlipidemia	1.17	0.65–2.06	0.5901	-	-	-
Malignancy	3.21	1.75–6.25	0.0003	2.09	1.08–4.25	0.0331
Current tobacco smoker	0.73	0.38–1.35	0.3291	-	-	-
Steroid administered	4.11	0.89–21.2	0.0684	-	-	-
Anticoagulant administered	1.99	1.06–3.69	0.0303	1.15	0.58–2.26	0.6791

OR, odds ratio; CI, confidence interval; BMI, body mass index; -, not available.

Table 4. Univariate and multivariate analyses of clinical factors for preoperative DVT

Variable	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Age >70 y	2.81	1.12–7.19	0.0270	2.63	1.04–6.80	0.0405
BMI >30 kg/m^2	2.92	0.43–11.98	0.1839	-	-	-
Male, sex	2.14	0.83–5.35	0.1039	-	-	-
Hypertension	0.73	0.29–1.84	0.5037	-	-	-
Diabetes mellitus	0.77	0.18–2.39	0.683	-	-	-
Hyperlipidemia	1.64	0.60–4.17	0.3076	-	-	-
Malignancy	1.86	0.93–4.75	0.1203	-	-	-
Current tobacco smoker	0.36	0.06–1.28	0.1756	-	-	-
Steroid administered	6.56	0.90–32.8	0.0309	5.34	0.71–27.87	0.0604
Anticoagulant administered	0.84	0.19–2.62	0.7891	-	-	-

DVT, deep vein thrombosis; OR, odds ratio; CI, confidence interval; BMI, body mass index; -, not available.

sis, patients' age >70 years (odds ratio, 2.93; 95% confidence interval, 1.64–5.31; p=0.0003) and patients with malignant disease (odds ratio, 2.09; 95% confidence interval, 1.08–4.25; p=0.0331) remained an independent predictor in the multivariate analysis (Table 3).

In addition, among the significant predictors for pre-DVT identified by univariate analysis, patients' age >70 years (odds ratio, 2.63; 95% confidence interval, 1.04–6.80; p=0.0405) remained an independent predictor in the multivariate analysis (Table 4).

ROC curve analysis revealed a cutoff D-dimer level of 1.8 μg/mL for a sensitivity and specificity of 70.5% and 65.0%, respectively (Fig. 2). When the cutoff value was applied at 1.8 μg/mL, the PPV was raised to 40.7% for predicting pre-DVT among patients with elevated D-dimer levels.

Patients with a diagnosis of pre-DVT who were prescribed DOAC, such as Edoxaban or Apixaban for 3 weeks were confirmed to have regression of the thrombus and did not require IPC during the perioperative period. None of the study patients developed bleeding complications due to anticoagulant therapy.

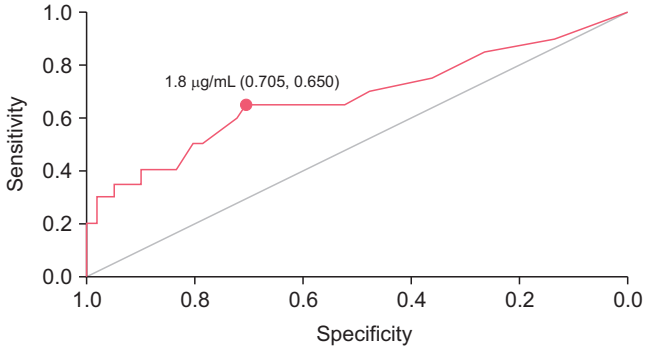

Fig. 2. Receiver operating characteristic (ROC) curve with cut-off point for D-dimer level.

Finally, all of the patients with pre-DVT underwent urological surgery. During a postoperative clinical follow-up period of 90 days, no patient developed symptomatic VTE.

DISCUSSION

VTE is one of the most common causes of perioperative death and should be prevented or identified as soon as possible. A previous study of patients undergoing surgery for femoral neck fractures reported that the majority of patients identified with postoperative DVT already had a thrombus before surgery [5]. In that study, the patients who developed pulmonary embolism had a relatively small thrombus in the soleal and gastrocnemius intramuscular venous plexi. Therefore, small peripheral DVTs should be taken seriously, and the use of IPC should be avoided in order to prevent postoperative VTE. The Caprini risk assessment model for postoperative VTE, which was introduced in 1991 [6], has been validated in over 250,000 patients in more than 100 worldwide clinical trials [7]. However, data on the presence of pre-DVT in patients undergoing urological surgery are limited. In this study, we determined an incidence of pre-DVT of 6.3% in 320 patients undergoing urological surgery. With regard to a screening method for DVT, the D-dimer test is easy to perform and useful for outpatients. Because of its high negative predictive value and high sensitivity, we use the D-dimer test to rule out DVT. However, its poor specificity requires additional diagnostic evaluations such as lower-limb venous CUS [8]. Taira et al. [9] reported that patients with a negative D-dimer (<0.5 μg/mL) test who are at low risk for DVT might not require additional costly imaging studies. However, the appropriate cutoff values of D-dimer for ruling out DVT remain unclear. In this study, we set a D-dimer cutoff value of 1.0 μg/mL, which is the upper limit of the reference value at our hospital lab for screening pre-DVT by lower-limb venous CUS. Therefore, we cannot be certain that DVT is absent in patients with low preoperative D-dimer level (between 0.5 and 1.0 μg/mL).

Also, little is also known about the correlation of pre-DVT with postoperative VTE in patients undergoing urological surgery. Schomburg et al. [10] found a high rate of subclinical DVT (13.9%) in the precystectomy population. Some of these DVTs may progress to VTE during the postoperative period, because VTE is common after radical cystectomy (2%–9%) [10,11]. In our study, we also found high rates of pre-DVT in patients with kidney (13.4%) and bladder cancer (8.7%); however, none of the patients developed symptomatic VTE after surgery after surgery as was reported in the previous reports [6,7]. Of course, not only pre-DVT but also other factors such as medications, surgery, and length of hospital stay must be considered as causes of postoperative VTE. Various patient's cares during the perioperative period might lead to decreased incidence of postoperative VTE even in patients with pre-DVT.

Regarding the clinical factors related to pre-DVT, in previous studies, some clinical risk factors related to pre-DVT have been reported. Patients with increased age, rheumatoid arthritis, a history of major surgery, and history of cancer treatment may be at an increased risk of pre-DVT in patients undergoing total hip arthroplasty [12]. Elderly people aged >75 years, female sex, and D-dimer ≥1.0 μg/mL were risk factors in patients with colorectal cancer [13]. In general, patients with history of DVT, steroid administered, thrombophilia like high phospholipid antibody syndrome are specific indications for pre-DVT screening. In our study, multivariate analysis of candidate clinical characteristics related to pre-DVT showed that age >70 years was a risk factor. Therefore, an elderly patient seems to be at considerable risk for pre-DVT before urological surgery, and preoperative screening by CUS for DVT should be applied to the elderly patient. However, those patients undergoing short time surgery, who does not require perioperative IPC because of the very low risk of perioperative VTE, could be excluded from this screening.

The screening fee for CUS is approximately 40 US dollars per patient in Japan. Furthermore, it takes 30 minutes per patient to screen DVT by CUS. The real benefit of DVT screening test is to avoid postoperative VTE which may be caused by perioperative IPC. However, it might be necessary to set new indications in order to reduce cost and time for it. Considering the cost- and time-effectiveness of screening, it might be useful to establish a D-dimer cutoff value to ≥1.8 μg/mL for screening, because the PPV was raised to 40.7% for detecting pre-DVT in our cohort. Understanding the presence of pre-DVT might help us to determine the indications for preoperative anticoagulant therapy and avoiding the use of perioperative IPC.

The limitations of this study are the small sample size and retrospective design. Therefore, further studies are needed to clarify the correlation between pre-DVT and postoperative VTE.

CONCLUSIONS

There was a high incidence of pre-DVT in patients undergoing urological surgery. This study proposes the specific indications of the patients who should undergo pre-DVT screening by CUS (age of >70 years and/or D-dimer ≥1.8 μg/mL). DOAC treatment for patients with pre-DVT and no use of IPC for those patients might prevent postoperative VTE.

https://doi.org/10.4111/icu.20200300

CONFLICTS OF INTEREST

The authors have nothing to disclose.

ACKNOWLEDGMENTS

We would like to thank all the patients who participated in this study.

AUTHORS' CONTRIBUTIONS

Research conception and design: Shuichi Tatarano. Data acquisition: Masaya Yonemori, Rumiko Eura, and Hirofumi Yoshino. Data analysis: HIroaki Nishimura. Interpretation and critical revision of the manuscript: Hideki Enokida. Supervision: Yasutoshi Yamada. Approval of the final manuscript: Masayuki Nakagawa.

SUPPLEMENTARY MATERIAL

Supplementary material can be found via https://doi.org/10.4111/icu.20200300.

REFERENCES

1. Tyson MD, Castle EP, Humphreys MR, Andrews PE. Venous thromboembolism after urological surgery. J Urol 2014;192:793-7.
2. McAlpine K, Breau RH, Mallick R, Cnossen S, Cagiannos I, Morash C, et al. Current guidelines do not sufficiently discriminate venous thromboembolism risk in urology. Urol Oncol 2017;35:457.e1-8.
3. Siddiqui AU, Buchman TG, Hotchkiss RS. Pulmonary embolism as a consequence of applying sequential compression device on legs in a patient asymptomatic of deep vein thrombosis. Anesthesiology 2000;92:880-2.
4. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013;48:452-8.
5. Song K, Yao Y, Rong Z, Shen Y, Zheng M, Jiang Q. The preoperative incidence of deep vein thrombosis (DVT) and its correlation with postoperative DVT in patients undergoing elective surgery for femoral neck fractures. Arch Orthop Trauma Surg 2016;136:1459-64.
6. Caprini JA, Arcelus JI, Hasty JH, Tamhane AC, Fabrega F. Clinical assessment of venous thromboembolic risk in surgical patients. Semin Thromb Hemost 1991;17 Suppl 3:304-12.
7. Cronin M, Dengler N, Krauss ES, Segal A, Wei N, Daly M, et al. Completion of the updated Caprini risk assessment model (2013 version). Clin Appl Thromb Hemost 2019;25:1076029619838052.
8. Righini M, Perrier A, De Moerloose P, Bounameaux H. D-Dimer for venous thromboembolism diagnosis: 20 years later. J Thromb Haemost 2008;6:1059-71.
9. Taira T, Taira BR, Carmen M, Chohan J, Singer AJ. Risk of venous thromboembolism in patients with borderline quantitative D-dimer levels. Am J Emerg Med 2010;28:450-3.
10. Schomburg JL, Krishna S, Cotter KJ, Soubra A, Rao A, Konety BR. Preoperative incidence of deep venous thrombosis in patients with bladder cancer undergoing radical cystectomy. Urology 2018;116:120-4.
11. Gangireddy C, Rectenwald JR, Upchurch GR, Wakefield TW, Khuri S, Henderson WG, et al. Risk factors and clinical impact of postoperative symptomatic venous thromboembolism. J Vasc Surg 2007;45:335-41; discussion 341-2.
12. Wakabayashi H, Hasegawa M, Niimi R, Sudo A. Clinical analysis of preoperative deep vein thrombosis risk factors in patients undergoing total hip arthroplasty. Thromb Res 2015;136:855-8.
13. Nakagawa K, Watanabe J, Suwa Y, Suzuki S, Ishibe A, Ota M, et al. Clinical analysis of preoperative deep vein thrombosis risk factors in patients with colorectal cancer: retrospective observational study. Ann Gastroenterol Surg 2019;3:451-8.