Original Articles

Title

A new pre-test probability score for diagnosis of deep vein thrombosis in patients before surgery

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Keywords

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Abstract

Background: Venous thromboembolism is a serious perioperative complication. We developed a new pre-test probability score for predicting deep vein thrombosis (DVT) before surgery.

Methods: Whole leg ultrasonography was performed on 973 inpatients and outpatients with suspected DVT based on a preoperative D-dimer cut-off value of ≥ 1 μg/ml. We allocated two-thirds (n=651) of the study participants to a derivation cohort and one-third (n=322) to a validation cohort. The pre-test probability model was developed from the derivation cohort data.

Results: The pre-test probability model for DVT assigned 2 points to D-dimer ≥ 1.5 μg/mL and 1 point each to age ≥ 60 years, female sex, ongoing glucocorticoid therapy, prolonged immobility, and cancer with high risk of DVT. The area under the curve of the pre-test probability score was 0.72 and 0.70 in the derivation and validation cohorts, respectively. The rates of DVT according to pre-test probability scores in the derivation and validation cohorts were 7% and 6% in the low (score =0-2), 23% and 22% in the intermediate (score =3-4), and 47% and 50% in the high probability group (score ≥5), respectively (P<0.0001).

Conclusions: The pre-test probability score (Kagoshima-DVT score) was helpful in

detecting preoperative DVT in both inpatients and outpatients. We identified low probability group to reduce whole-leg ultrasonography and high probability group to detect more DVT before surgery.

Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT), and pulmonary thromboembolism (PTE), is a serious perioperative complication that causes morbidity and mortality to hospital patients [1]. Approximately 80% of PTE results from DVT in the lower extremities [2], and asymptomatic DVT is often observed. However, once PTE occurs, the in-hospital mortality rate is reported to be 14% in Japan [3], and perioperative PTE is associated with high 30-day mortality [4]. Therefore, we should detect DVT preoperatively as much as possible and intervene early or prevent the development of VTE.

The 9th American College of Chest Physicians recommends the Wells Score to estimate the preclinical risk of DVT [5-6]. The Wells score is most widely used and incorporates signs, symptoms, and risk factors of VTE to categorize the probability of DVT in the lower extremity into low, intermediate, or high probability. In patients with a low or intermediate risk of DVT, the measurement of D-dimer level is recommended. If the D-dimer is positive, further testing with whole-leg ultrasonography (WLUS) is suggested. However, in patients with a high risk of DVT, the recommendation is to perform WLUS without measuring D-dimer levels. Recently, WLUS is useful for diagnosing DVT because it is easily accessible, non-invasive, and has a high specificity

of 96% [6]. However, WULS is not commonly performed on D-dimer-positive patients before surgery as it is time-consuming, expensive, and requires proficient clinical skills. In our facility, D-dimer levels were measured in all preoperative cases, even in the absence of symptoms. If the D-dimer was positive (D-dimer ≥ 1.0 μg/ml), WLUS was performed in all patients as part of DVT screening. However, the low detection rate of DVT was a problem.

Therefore, we aimed to develop a pre-test probability score for predicting DVT before surgery using highly objective perioperative clinical and laboratory variables and stratify patients into perioperative DVT probability groups.

Materials and Methods

Study Population

This study was a retrospective cohort study, which included a total of 7,435 patients who were planed surgery under general anesthesia at Kagoshima University between January 2017 and December 2018. The inpatients and outpatients with a cut-off value ≥ 1 μg/ml of D-dimer, which were measured routinely before surgery in our facility, were referred to cardiologists for suspicion of DVT. We performed WLUS on 1,305 inpatients and outpatients with suspected DVT. 332 patients were excluded due to the following reasons: aneurysm, n=131; pregnancy, n=115; ongoing anticoagulant therapy, n=50; central venous catheter, indwelling drain, n=16; poor image, n=6; another thrombosis, n=5; disseminated intravascular coagulation, n=3; age < 18 years, n=3; factor V deficiency, n=1; protein C deficiency, n=1; factor V deficiency, n=1; haemophilia, n=1. We defined aneurysms as thoracic aortic aneurysms, abdominal aortic aneurysms, and common iliac artery aneurysms. Patients with aneurysms were excluded because of the presence of intramural thrombus. Besides, pregnant women were excluded because pregnancy is a known risk factor for DVT, and prevention measures had been provided from early pregnancy. We excluded the patients with central venous catheter or indwelling drain because of the increased D-dimer associated with drainage

procedures. Finally, 973 patients were included in this study (Figure 1).

We used a split-sample method to derive and independently validate a new pre-test probability score for DVT diagnosis before surgery. We randomly allocated two-thirds (n=651) of the study participant to a derivation cohort and one-third (n=322) to a validation cohort.

Ethical approval was obtained from the Ethics Committee of Kagoshima University (Ref: 150279 [27-205]). The board has abandoned the need for informed consent because this study has a retrospective nature, and the personal data has been de-identified. All processes complied with the guidelines of the Declaration of Helsinki of 1975, as revised in 2000.

Procedures and definitions

We assessed 17 clinical variables known to be risk factors for DVT, as reported previously. Clinical variables were retrospectively collected from the nursing and medical records. Brain, pancreas, gastric, colorectal, lung, kidney, bone, ovarian, and uterine cancers, lymphoma, and myeloma were defined as cancer with a high risk of DVT [7-8]. Prolonged immobility was defined as the need for full assistance for more than three days during transfer. Diabetes mellitus was defined by glycated hemoglobin ≥

6.5%, fasting plasma glucose ≥ 126 mg/dl, random plasma glucose ≥ 200 mg/dl, or antidiabetic medical treatment. Hypertension and hyperuricemia were defined by the relevant medical treatment. Antipsychotic drugs were included olanzapine, haloperidol, sulpiride, risperidone, aripiprazole, quetiapine, and perospirone with DVT side effects listed in the drug information. Glucocorticoids were included the oral medications of prednisolone, hydrocortisone, betamethasone**,** and dexamethasone. Regarding laboratory variables, we assessed seven factors related to DVT occurrence previously reported as follows: white blood cell, hemoglobin, platelet, estimated glomerular filtration rate (eGFR), aspartate aminotransferase (AST), alanine transaminase (ALT), and D-dimer. Preoperative laboratory tests were performed within one month of referral to our cardiology department. We measured plasma D-dimer levels by a latex agglutination assay (LPIA-ACE D-dimer II, LSI Medience Corporation, Tokyo, Japan).

Ultrasonography

We diagnosed DVT using B-mode, color Doppler, and pulsed Doppler ultrasonography. The basic techniques were the venous compression test with a probe, the milking test with manual compression and decompression of the lower extremity, and a respiratory stress test with abdominal breathing to induce blood flow. We scanned the patients from

the common iliac vein to the ankle, with a focus on the deep and superficial veins. We defined the central side as the area ranging from the common iliac vein to the popliteal vein and the peripheral side as the area distal to the popliteal vein. We examined the patients using a linear probe (5-9 MHz) and a convex probe (2-4 MHz) (Pro-Sound F 75, Pro-Sound Alpha 7, ARIETTA 70; Hitachi Aloka Medical, Tokyo, Japan). All examinations were performed by three doctors, who were ultrasound specialists certified by the Japan Society of Ultrasonics in Medicine, and six clinical technologists, who were ultrasound technicians certified by the Japanese Society of Sonographers. All echo images were discussed at a multi-participant conference to determine the diagnosis. We identified fresh DVT as a homogenous, soft, compressible hypoechoic thrombus within an enlarged vein or a floating thrombus. We identified chronic DVT as a heterogeneous, hard, non-deformable hyperechoic thrombus within a narrowed vein.

Statistical Analysis

Continuous variables were dichotomized into categorical variables to develop a pre-test probability model. The cut-off values for age ≥ 60 years, body mass index (BMI) ≥ 25 kg/m^2, white blood cells ≥ 11000 /μL, hemoglobin ≤ 10 g/dL, platelet count ≥ 350000 /μL, and D-dimer ≥ 1.5 μg/mL were derived from a previous report [9-10]. The cut-off

value for the estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 m^2, aspartate aminotransferase (AST) ≥ 40 IU/L, and alanine aminotransferase (ALT) ≥ 40 IU/L were derived from the upper limit of normal reference values.

We compared categorical variables between the cohorts using the χ 2 test, continuous variables using the Wilcoxon rank-sum test or t-test. The pre-test probability score was developed from the derivation cohort data. A univariate logistic regression model was developed to assess the association between 24 variables and the presence of DVT events in the derivation cohort. Data were unavailable for five patients regarding AST and ALT, for two patients regarding white blood cells, hemoglobin, and platelets, and for one patient regarding BMI. We included variables using P-value < 0.1 in the univariate logistic regression model into the multivariate model. The backward model selection method was applied to remove variables that were not associated with DVT. A multivariate logistic regression model was developed using the variables with P-value< 0.05 for the presence of DVT. We developed a pre-test probability model using the results of the multivariate logistic regression models [11], where we divided the respective β coefficient by the smallest β coefficient and rounded to the nearest point for the variable. The accuracy of the pre-test probability scores in the derivation and validation cohorts was evaluated by receiver operating characteristic curve analysis

[12]. We stratified the distribution of respectively pre-test probability score of patients into three probability categories according to the level of DVT probability: low, intermediate, and high. JMP® 15 (SAS Institute Inc., Cary, NC, USA) and R (version 4.0.2; The R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis.

Results

Characteristics of participants

In table 1, we show clinical and laboratory characteristics of the derivation and validation cohorts. Patients in the derivation cohort were more likely to have diabetes mellitus and prolonged immobility than those in the validation cohort. DVT was observed in 205 (21.1%) patients in the total population, 138 patients (21.2%) and 67 patients (20.8%) in derivation and validation cohorts, respectively. There were 102 patients (10.5%) with fresh DVT: 71 patients (10.9%) and 31 patients (9.6%), respectively. DVT was detected more peripherally than centrally. DVT on the central side was observed in 25 patients (2.6%): 19 patients (2.9%) and six patients (1.9%), respectively. DVT on the peripheral side was observed in 190 patients (19.5%): 127 patients (19.5%) and 63 patients (19.5%), respectively. DVT on the central and peripheral side was observed in 12 patients (1.2%): 10 patients (1.5%) and 2 patients (0.6%), respectively (Table 2). Besides, DVT was more prevalent in the left extremities than in the right extremities, with 169 patients on the left and 140 patients. DVT was most frequently detected in the soleus vein in both the right and left extremities (Figure 2). Most patients in the cohort had been referred to the cardiologist by gastroenterologists (23.3%) and orthopaedists (22.7%) (Online Figure 1).

Kagoshima-DVT scoring method and assessment

The pre-test probability model for DVT assigned 2 points to D-dimer ≥ 1.5 μg/mL and 1 point each to age ≥ 60 years, female sex, ongoing glucocorticoid therapy, cancer with high risk of DVT, and prolonged immobility (Table 3). The pre-test probability scores (Kagoshima-DVT score) for DVT ranged from 0 to 7 (Figure 3A). The area under the curve (AUC) of the pre-test probability score for DVT was 0.72 and 0.70 in the derivation and validation cohorts, respectively.

The AUC of the pre-test probability scores for DVT in the derivation and validation cohorts demonstrated modest accuracy, with AUC ranging from 0.6–0.75.

There was no significant difference in the AUC for the DVT probability score between both cohorts (P=0.75). Patients were stratified by DVT score into high (score ≥5 points), intermediate (score 3–4 points), and low (0–2 points) probability groups. In the derivation cohort, the rate of DVT was high in the high probability group than in the intermediate and low probability groups (47%, 23%, and 7%, respectively; P<0.0001). The same trend was observed in the validation cohort (50%, 22%, and 6%, respectively; P<0.0001) (Figure 3B). In the derivation cohort, the rate of fresh DVT was high in the high probability group than in the intermediate and low probability groups (33%, 10%,

and 1%, respectively; P<0.0001). The same trend was observed in the validation cohort (19%, 9%, and 3%, respectively; P<0.0001) (Online Figure 2).

Furthermore, as a sensitivity analysis, we developed a pre-test probability model for DVT using a D-dimer cut-off value of ≥ 2 μg/mL instead of ≥ 1.5 μg/mL. The pre-test probability model for DVT was assigned 1 point each for D-dimer ≥ 2 μg/mL, age ≥ 60 years, female sex, ongoing glucocorticoid therapy, prolonged immobility, and cancer with high risk of DVT. The AUC of the pre-test probability score for DVT score was 0.717 in the derivation cohort. There was no significant difference between the AUC of D-dimer cut-off values ≥ 1.5 μg/mL and ≥ 2 μg/mL (Online Figure 3).

Discussion

Our study showed that one laboratory variable (D-dimer ≥ 1.5 μg/mL) and five clinical variables (age ≥ 60 years, female sex, ongoing glucocorticoid therapy, cancer with high risk of DVT, and prolonged immobility) are independently associated with DVT in inpatients and outpatients before surgery under general anesthesia. Moreover, it demonstrates that a pre-test probability (Kagoshima-DVT score) score can help detect DVT before surgery according to the probability group. We recommend WLUS in preoperative patients with Kagoshima-DVT score ≥ 3 (intermediate or high groups).

The comparison between previous scores and Kagoshima-DVT score

The Wells score, Oudega score, and Hamilton score were developed as pre-test probability scores for DVT. The Wells score was not correctly validated in primary care or preoperatively; thus, the Oudega score with the addition of D-dimers was proposed as an alternative to the Wells score for primary care patients [13]. However, in the Wells score and Oudega score, a lower extremity venous ultrasound was performed on the central side only, and DVT below the knee was unknown. In contrast, the Hamilton score was developed for ambulatory patients [14], and venous ultrasonography was performed for the symptomatic lower extremity only. The combination of negative D-

dimer and a low Hamilton score had a high negative predictive value and could exclude DVT [15]. An alternative to the previous scores is the unique and novel Kagoshima-DVT score, which can detect preoperative asymptomatic DVT.

The Wells score and the Hamilton score had the item, “the patient was recently bedridden for at least three days or had major surgery in the prior 12 weeks necessitating general or regional anesthesia.” However, our study did not incorporate the item, “major surgery in the prior 12 weeks necessitating general or regional anesthesia.” Instead, we referred to the nursing records and defined patients with prolonged immobility as those who required full assistance during transfer for more than three days instead of patients who were recently bedridden for at least three days.

The Wells score mainly aimed to detect symptomatic DVT. However, asymptomatic DVT is common in preoperative patients, and physical examination might not be helpful in detecting DVT in such patients [16]. In addition, physical examination is less objective and less accurate as it depends on the judgment of the medical professional. Therefore, we did not include physical examination in the Kagoshima DVT score. The high objectivity of our score was maintained, as it was calculated using objective variables only (Online Table 1).

D-dimer

D-dimer is a globally used indicator of the coagulation-fibrinolysis system. Several studies have shown that D-dimer is a valuable biomarker for DVT diagnosis and management [17-18]. D-dimer is measured using several methods, including latex agglutination assay and enzyme-linked immunosorbent assay (ELISA). These methods have a high sensitivity, moderate specificity for DVT; thus, they can certainly exclude DVT [19].

A previous study showed a D-dimer cut-off value for DVT before treatment in ovarian cancer was 1.5 μg/mL, and its sensitivity and specificity are 100% and 61.6%, respectively [20]. Another study reported that 75% of patients with cancer had elevated D-dimer ≥ 1.44 μg/mL and were significantly at a greater risk of VTE than those with lower D-dimer levels [10]. Since our study population included 568 cancer patients (58.3%), we used a D-dimer cut-off value of ≥ 1.5 μg/mL for suspicion of DVT to calculate the Kagoshima-DVT score. As a sensitivity analysis, we re-analyzed the score using a D-dimer cut-off value of ≥ 2.0 μg/mL, but the results were not significantly different; thus, we adopted a D-dimer cut-off value of ≥ 1.5 μg/mL.

Other associated factors

The risk factors assessed in our study have been reported previously. First, older age was associated with VTE, as in a previous report [21]. Patients aged ≥ 60 years undergoing non-major surgery had an intermediate risk of perioperative VTE [22]. For this reason, age ≥ 60 years was used to calculate the Kagoshima-DVT score. Second, the rate of acute PTE was higher in women than in men in Japan [23]. Similarly, in our study, the rate of DVT was higher in women than in men. Third, glucocorticoid therapy had a side effect of DVT [24] and was a preoperative factor associated with symptomatic VTE [25]. An experimental study showed a rapid effect of glucocorticoids on clotting factor levels [26]. However, obesity is known as a risk factor for VTE in the general population [27], but the variable of BMI ≥ 25 kg/m^2 did not show statistical significance in this study. Considering that more than half of the patients had cancer and were, therefore, underweight and had poor nutritional status, the effect of weight on DVT risk might have been modified.

Clinical implication

We stratified the DVT probability into low, intermediate, and high groups before surgery. We identified low probability group to reduce whole-leg ultrasonography and high probability group to detect more DVT before surgery. Therefore, it is useful to use

the Kagoshima-DVT score for the exclusion diagnosis of DVT before surgery.

Limitations

This study had several limitations. First, this retrospective study was performed at a single medical center. However, as a university hospital, various surgeries are performed, and preoperative examinations are performed appropriately and accurately according to the protocol set by the anesthesiology department. Therefore, being a single institution made it possible to collect accurate data. Second, since this study was conducted in preoperative Japanese patients with D-dimer levels ≥ 1 μg/ml, further validation is needed to determine whether it is applicable to the general population. However, the addition of five clinical variables to the D-dimer cut-off value ≥ 1.5 μg/ml, the pre-test probability score may be adapted for detecting DVT in all patients before surgery more efficiently. Third, few patients were included in the validation cohort. Nevertheless, the results in the derivation and validation cohorts were consistent, and we believe that the number of cases was sufficient for the current analysis. Further prospective multi-center research is needed to validate these findings.

Conclusion

We developed a pre-test probability (Kagoshima-DVT score) score for predicting DVT before surgery under general anesthesia using one laboratory (D-dimer, ≥ 1.5 μg/mL) and five clinical variables (age ≥ 60 years, female sex, ongoing glucocorticoid therapy, cancer with high risk of DVT, and prolonged immobility) for inpatients and outpatients. We stratified the DVT probability into low, intermediate, and high groups before surgery. We identified low probability group to reduce whole-leg ultrasonography and high probability group to detect more DVT before surgery.

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Finding

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Disclosures

The Authors declare that there is no conflict of interest.

References

[1] Nakamura M, Yamada N, Ito M. Current management of venous thromboembolism in Japan: current epidemiology and advances in anticoagulant therapy. J Cardiol 2015; 66: 451–9.

[2] Tapson VF. Acute pulmonary embolism. N Engl J Med 2008; 358: 1037-52.

[3] Nakamura M, Sakuma M, Yamada N, Tanabe N, Nakanishi N, Miyahara Y, et al. Risk factors of acute pulmonary thromboembolism in Japanese patients hospitalized for medical illness: results of a multicenter registry in the Japanese society of pulmonary embolism research. J Thromb Thrombolysis 2006; 21: 131-5.

[4] Comfere TB, Sprung J, Case KA, Dye PT, Johnson JL, Hall BA, et al. Predictors of mortality following symptomatic pulmonary embolism in patients undergoing noncardiac surgery. Can J Anaesth 2007; 54: 634-41.

[5] Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, et al. Evaluation of D-dimer in the diagnosis of suspected deep vein thrombosis. N Engl J Med 2003; 349: 1227–35.

[6] Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians

Evidence-Based Clinical Practice Guidelines. Chest 2012; 141 Suppl 2: e419S–96S.

[7] Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie N, et al. Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014; 35: 3033–69.

[8] Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 2008; 111: 4902–7.

[9] 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.

[10] Ay C, Dunkler D, Marosi C, Chiriac AL, Vormittag R, Simanek R, et al. Prediction of venous thromboembolism in cancer patients. Blood 2010; 116: 5377–82.

[11] Tu JV, Naylor CD. Clinical prediction rules. J Clin Epidemiol 1997; 50: 743–4.

[12] Metz CE. Basic principles of ROC analysis. Semin Nucl Med 1978; 8: 283–98.

[13] Oudega R, Hoes AW, Moons KG. The Wells rule does not adequately rule out

deep venous thrombosis in primary care patients. Ann Intern Med 2005; 143: 100–7.

[14] Constans J, Boutinet C, Salmi JR, Saby JC, Nelzy ML, Baudouin P, et al. Comparison of four clinical prediction scores for the diagnosis of lower limb deep venous thrombosis in outpatients. Am J Med 2003; 115: 436–40.

[15] Subramaniam RM, Chou T, Heath R, Allen R. Importance of pretest probability score and D-dimer assay before sonography for lower limb deep venous thrombosis. Am J Roentgenol 2006; 186: 206–12.

[16] 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.

[17] Stein PD, Hull RD, Patel KC, Olson RE, Ghali WA, Brant R, et al. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. Ann Intern Med 2004; 140: 589–602.

[18] Bozic M, Blinc A, Stegnar M. D-dimer, other markers of haemostasis activation and soluble adhesion molecules in patients with different clinical probabilities of deep vein thrombosis. Thromb Res 2002; 108: 107–14.

[19] Yamaki T, Nozaki M, Sakurai H, kikuchi Y, Soejima K, Kono T, et al. Combined use of pretest clinical probability score and latex agglutination D-dimer testing for excluding acute deep vein thrombosis. J Vasc Surg 2009; 50: 1099–105.

[20] Kawaguchi R, Furukawa N, Kobayashi H. Cut-off value of D-dimer for prediction of deep venous thrombosis before treatment in ovarian cancer. J Gynecol Oncol 2012; 23: 98–102.

[21] Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA 2005; 293: 715–22.

[22] Nakamura M, Miyata T, Ozeki Y, Takayama M, Komori K, Yamada N, et al. Current venous thromboembolism management and outcomes in Japan. Circ J 2014; 78: 708–17.

[23] Nakamura M, Fujioka H, Yamada N, Sakuma M, Okada O, Nakanishi N, et al. Clinical characteristics of acute pulmonary thromboembolism in Japan: results of a multicenter registry in the Japanese Society of Pulmonary Embolism Research. Clin Cardiol 2001; 24: 132–8.

[24] Chaudhuri MD, Bhan GL. Deep vein thrombosis: a side effect of steroid therapy. Br J Clin Pract 1984; 38: 118–9.

[25] 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: 335–42.

[26] Zaane BV, Nur E, Squizzato A, Gerdes VEA, Büller HR, Dekkers OM, et al. Systematic review on the effect of glucocorticoid use on procoagulant, anti-coagulant and fibrinolytic factors. J Thromb Haemost 2010; 8: 2483–93.

[27] Ageno W, Squizzato A, Garcia D, Imberti D. Epidemiology and risk factors of venous thromboembolism. Semin Thromb Hemost 2006; 32: 651–8.

Tables

Table 1. Clinical and laboratory characteristics of the derivation and validation cohorts

	Derivation cohort (n=651)	Validation cohort (n=322)	P Values
Clinical variable			
Age, years	67.6±13.9	67.2±13.9	0.69
Age ≥ 60 years	508 (78%)	255 (79%)	0.68
In-patent	213 (33%)	98 (30%)	0.46
Female sex	329 (51%)	154 (49%)	0.43
Height cm	157.6±9.7	158.8±8.9	0.54
Body weight kg	57.9±12.4	58.6±12.7	0.42
BMI	23.2±4.1	23.4±4.2	0.59
BMI ≥ 25.0 kg/m^2	182 (28%)	99 (31%)	0.35
Diabetes mellitus	154 (24%)	98 (30%)	0.02
Hypertension	341 (52%)	174 (54%)	0.63
Hyperuricemia	62 (10%)	38 (12%)	0.27
Ongoing antiplatelet drug	98 (15%)	52 (16%)	0.66
Ongoing diuretic drug	59 (9%)	29 (9%)	0.98
Antipsychotic drug with side effect of DVT	41 (6%)	21 (7%)	0.89
Dialysis	33 (5%)	16 (5%)	0.72
Trauma	45 (7%)	26 (8%)	0.51
Ongoing glucocorticoids	50 (8%)	19 (6%)	0.31
History of DVT	7 (1%)	2 (1%)	0.48
Infection	43 (7%)	26 (8%)	0.40
Cancer with high risk of DVT	182 (28%)	102 (32%)	0.23
Prolonged immobility	45 (7%)	32 (10%)	0.034
Laboratory variable			
WBC ≥ 11000 /μL	34 (5%)	21 (7%)	0.41
Hb ≤ 10 g/dL	82 (13%)	48 (15%)	0.31
Plt ≥ 35000 /μL	59 (9%)	33 (10%)	0.55
eGFR ≤ 60 mL/min/1.73 m^2	246 (38%)	125 (39%)	0.76
AST ≥ 40 IU/L	63 (10%)	23 (7%)	0.19
ALT ≥ 40 IU/L	60 (9%)	20 (6%)	0.11
D-dimer ≥ 1.5 μg/mL	452 (69%)	220 (68%)	0.72

Continuous variables were expressed as mean ± standard derivation and categorical variables as number and percentage.

DVT, deep vein thrombosis; BMI, body mass index; WBC, white blood cell count; Hb, hemoglobin; Plt, platelet count; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 2. The number and proportion of the presence of DVT in the derivation and validation cohorts

	Derivation cohort (n=651)	Validation cohort (n=322)	Total (n=973)
DVT	138 (21.2%)	67 (20.8%)	205 (21.1%)
Fresh DVT	71 (10.9%)	31 (9.6%)	102 (10.5%)
Central DVT	19 (2.9%)	6 (1.9%)	25 (2.6%)
Peripheral DVT	127 (19.5%)	63 (19.5%)	190 (19.5%)
Proximal and distal DVT	10 (1.5%)	2 (0.6%)	12 (1.2%)

DVT, deep vein thrombosis.

Table 3. Univariate and multivariate logistic regression analysis for DVT probability in the derivation cohort

	Univariate analysis	P	Multivariate analysis		P	Score
	Odds ratio (95% CI)	Values	Odds ratio (95% CI)	β coefficient	Values	
Clinical variable						
Age ≥ 60 years	2.06 (1.22-3.48)	0.0059	2.33 (1.34-4.03)	0.85	0.0027	1
In-patent	1.28 (0.87-1.89)	0.21				
Female sex	2.16 (1.47-3.19)	< 0.001	2.15 (1.42-3.24)	0.77	0.0003	1
BMI ≥ 25.0 kg/m^2	0.85 (0.56-1.31)	0.47				
Diabetes mellitus	0.67 (0.42-1.08)	0.10				
Hypertension	1.12 (0.77-1.63)	0.55				
Hyperuricemia	0.76 (0.39-1.50)	0.43				
Ongoing antiplatelet drug	0.63 (0.35-1.13)	0.12				
Ongoing diuretic drug	1.39 (0.76-2.55)	0.29				
Antipsychotic drug with side effect of DVT	1.59 (0.74-3.41)	0.23				
Dialysis	0.83 (0.33-2.04)	0.68				
Trauma	1.18 (0.58-2.40)	0.64				
History of DVT	2.82 (0.62-12.8)	0.16				
Infection	0.98 (0.46-2.10)	0.96				
Ongoing glucocorticoids	1.98 (1.07-3.67)	0.0275	2.40 (1.23-4.70)	0.88	0.01	1
Cancer with high risk of DVT	2.01 (1.36-2.97)	0.0004	2.10 (1.37-3.20)	0.74	0.0007	1
Prolonged immobility	2.90 (1.55-5.41)	0.0005	2.49 (1.29-4.84)	0.92	0.0065	1
Laboratory variable						
WBC ≥ 11000 /μL	0.76 (0.31-1.88)	0.56				
Hb ≤ 10 g/dL	0.94 (0.53-1.66)	0.82				
Plt ≥ 35000 /μL	1.52 (0.84-2.77)	0.16				
eGFR ≤ 60 mL/min/1.73 m^2	1.10 (0.76-1.63)	0.59				
AST ≥ 40 IU/L	0.93 (0.49-1.76)	0.81				
ALT ≥ 40 IU/L	1.10 (0.59-2.07)	0.76				
D-dimer ≥ 1.5 μg/mL	3.50 (2.09-5.87)	< 0.001	3.14 (1.83-5.40)	1.14	<0.001	2

CI, confidence interval; DVT, deep vein thrombosis; BMI, body mass index; WBC, white blood

cell count; Hb, hemoglobin; Plt, platelet; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Figure legends

Figure 1. Study flow chart for developing and validating of the pre-test probability model.

DVT, deep vein thrombosis; DIC, disseminated intravascular coagulation.

Figure 2.

A. Thrombus area in the derivation and validation cohorts.

B. DVT by vein in the derivation and validation cohorts.

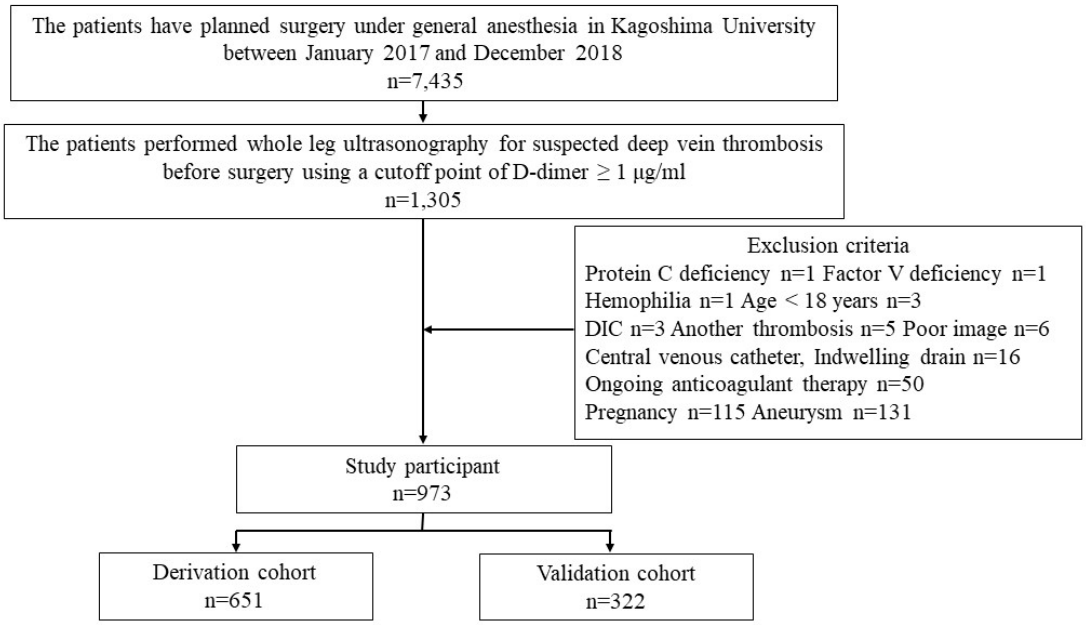
DVT, deep vein thrombosis.

Figure 3.

A. Element of pre-test probability score (Kagoshima-DVT score) for DVT before surgery.

B. Rates of DVT according to scores from the pre-test probability model in the derivation and validation cohorts.

DVT, deep vein thrombosis.



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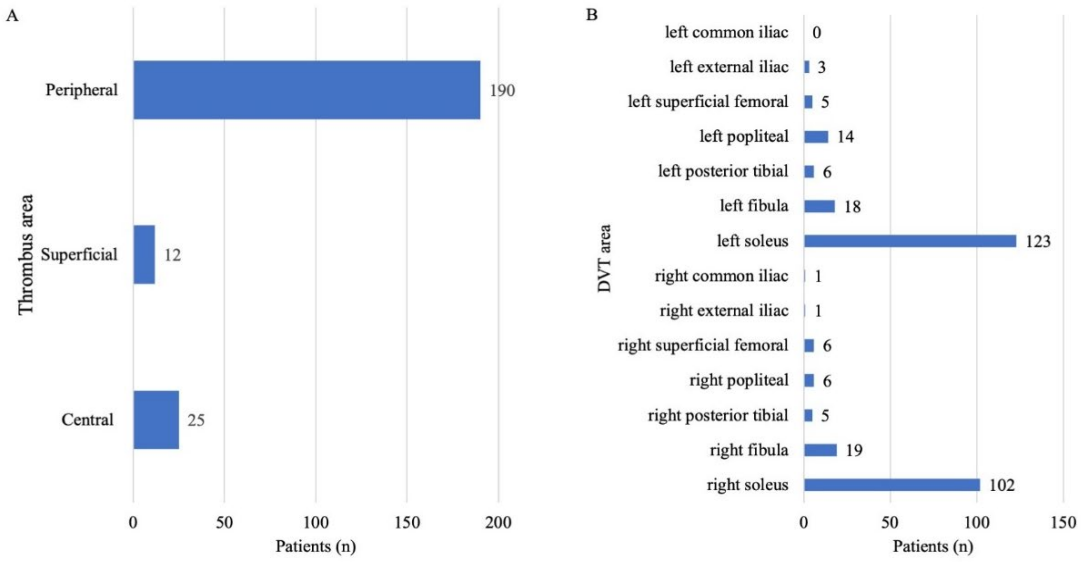

Figure 2.

A. Thrombus area in the derivation and validation cohorts.

B. DVT by vein in the derivation and validation cohorts.

DVT, deep vein thrombosis.

A

Variable	Points
D-dimer ≥ 1.5 μg/mL	2
Age ≥ 60 years	1
Female	1
Ongoing glucocorticoids	1
Cancer with high risk of DVT	1
Prolonged immobility	1
Total Score Range:0-7	

B

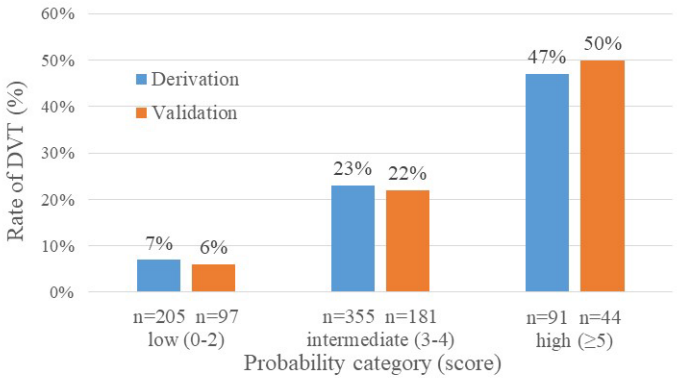

Figure 3.

A. Element of pre-test probability score (Kagoshima-DVT score) for DVT before surgery.

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DVT, deep vein thrombosis.

Supplementary materials

Supplementary Table and Figure

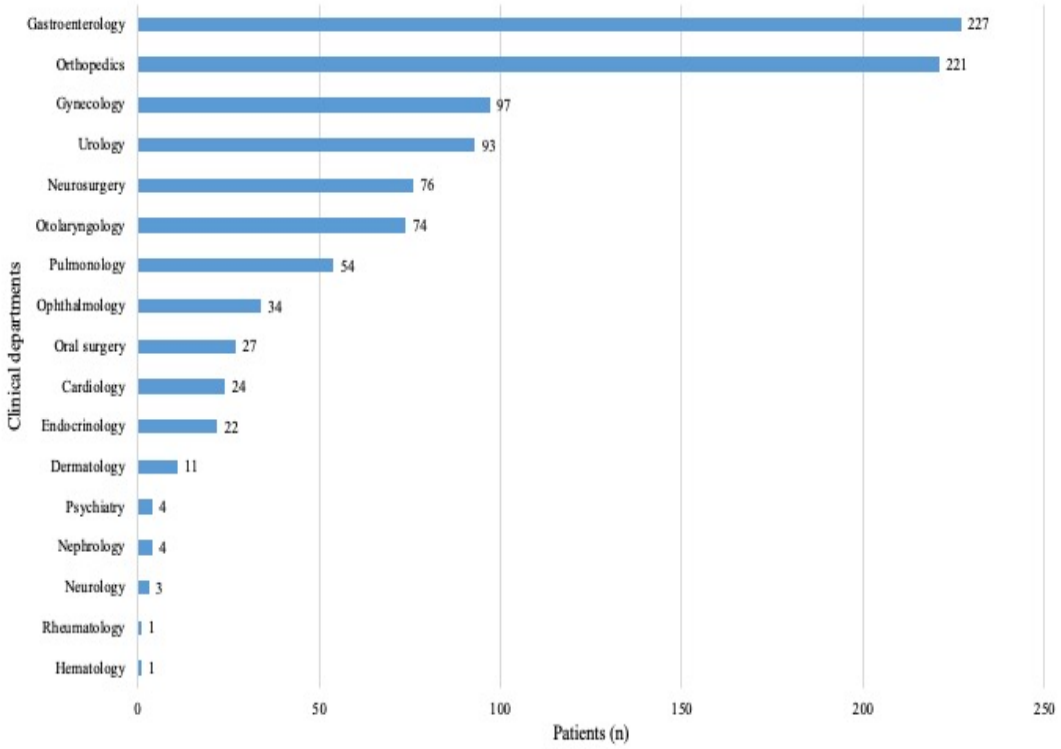
Online Table 1. Summary of probability assessment for DVT

Variable	Wells Score	HAMILTON Score	Kagoshima -DVT score
Active cancer with either palliative therapy or treatment that is either ongoing or within the prior 6 months	1	2	
Patient was recently bedridden for at least 3 days or major surgery in the prior 12 weeks necessitating general or regional anesthesia	1	1	
Recent plaster immobilization, paresis or paralysis of the lower extremities	1	2	
Tenderness that is localized along the distribution of the deep veins	1		
Leg is entirely swollen	1		
Discrepancy of ≥ 3 cm in calf circumference	1	1	
Pitting edema in the symptomatic leg	1		
Presence of collateral superficial non varicose veins	1		
There is an alternative diagnosis as likely as DVT	-2		
The emergency department physician has an elevated clinical suspicion of DVT in the absence of other possible alternative diagnoses		2	
Male		1	
Erythema		1	
D-dimer ≥ 1.5 μg/mL			2
Female			1
Age ≥ 60 years			1
Ongoing glucocorticoids			1
Cancer with high risk of DVT			1

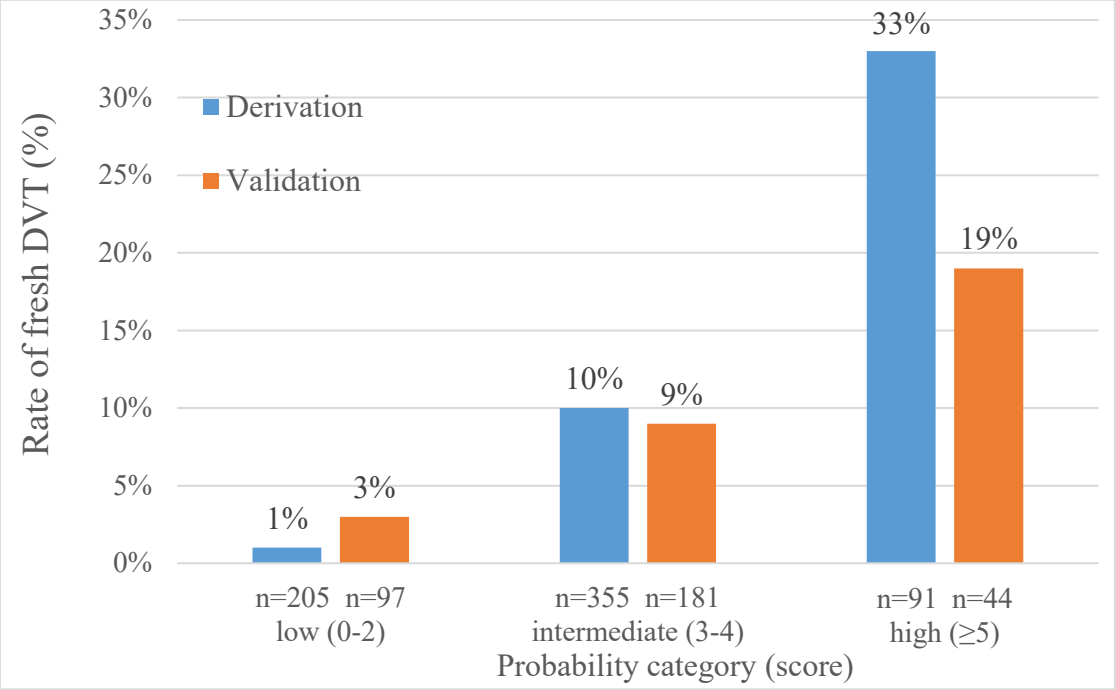
Prolonged immobility	1

DVT, deep vein thrombus.

Online Figure 1. Clinical departments of patients in the derivation and validation cohorts.



Online Figure 2. Rates of fresh DVT according to scores from the probability model in the derivation and the validation cohorts.

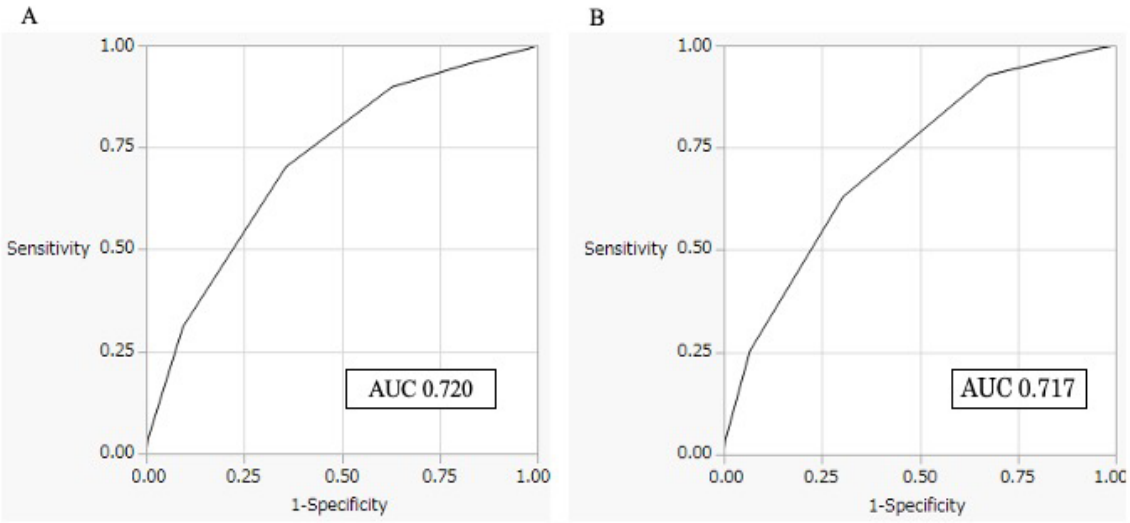


DVT, deep vein thrombosis

Online Figure 3

A. ROC curve for the pre-test probability score of D-dimer ≥ 1.5 μg/mL in the derivation cohort (AUC 0.720).

B. ROC curve for the pre-test probability score of D-dimer ≥ 2 μg/mL in the derivation cohort (AUC 0.717).



ROC, receiver operating characteristics; DVT, deep vein thrombosis; AUC, area under curve