**JKMS**

## Original Article
### Immunology, Allergic Disorders & Rheumatology

Check for updates

# Practical Utility of D-dimer Test for Venous Thromboembolism in Systemic Lupus Erythematosus Depends on Disease Activity: a Retrospective Cohort Study

OPEN ACCESS

**Yoon-Jeong Oh** [ID],[1] **Eun Hye Park** [ID],[2] **Jun Won Park** [ID],[3] **Yeong Wook Song** [ID],[3,4] **and Eun Bong Lee** [ID] [3,4,5]

[1]Division of Rheumatology, Department of Internal Medicine, Kangwon National University School of Medicine, Chuncheon, Korea
[2]Division of Rheumatology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea
[3]Division of Rheumatology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea
[4]Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology, Seoul National University, Seoul, Korea
[5]Wide River Institute of Immunology, Seoul National University College of Medicine, Hongcheon, Korea

**ORCID iDs**
Yoon-Jeong Oh [ID]
https://orcid.org/0000-0003-1028-3481
Eun Hye Park [ID]
https://orcid.org/0000-0002-6813-4182
Jun Won Park [ID]
https://orcid.org/0000-0002-8624-2582
Yeong Wook Song [ID]
https://orcid.org/0000-0002-5384-3437
Eun Bong Lee [ID]
https://orcid.org/0000-0003-0703-1208

## ABSTRACT

**Background:** The D-dimer test is a screening tool for venous thromboembolism (VTE); however, its utility for patients with systemic lupus erythematosus (SLE) remains unclear. Here, we examined the utility of the D-dimer test as a screening tool for VTE in SLE patients.
**Methods:** SLE patients (n = 276) and age- and sex-matched patients with non-rheumatic disease (n = 1,104), all of whom underwent D-dimer testing to screen for VTE, were enrolled. The sensitivity and specificity and receiver operating characteristics curve of the D-dimer test were compared in both groups. Then, subgroup of SLE patients in whom the D-dimer test can be useful was sought.
**Results:** The incidence of VTE was more common in SLE patients than controls (10.9% vs. 4.0%). Although the sensitivity of the D-dimer test was comparable between SLE patients and controls (93.3% vs. 90.9%), the specificity of the test was profoundly lower in SLE patients compared to controls (28.4% vs. 84.4%). The area under the curve (AUC) of the D-dimer for VTE was 0.669 in SLE patients and 0.90 in control group. Multiple linear regression analysis demonstrated that SLE disease activity index-2000 (SLEDAI-2K) was significantly associated with D-dimer levels in SLE patients ($\beta = 0.155$; $P = 0.022$). Subgroup analysis showed that the AUC is moderate (0.768) with low disease activity, while it is low (0.518) with high SLEDAI-2K.
**Conclusion:** The D-dimer test may not be a useful screening tool for VTE in patients with active SLE. D-dimer test for predicting VTE in SLE patients should be differentially applied according to disease activity of SLE.

**Keywords:** D-dimer; Venous Thromboembolism; Systemic Lupus Erythematosus; SLEDAI-2K

**Author Contributions**

Conceptualization: Lee EB. Data curation: Oh YJ, Park EH, Park JW. Formal analysis: Oh YJ. Investigation: Oh YJ. Project administration: Lee EB. Supervision: Lee EB. Writing - original draft: Oh YJ. Writing - review & editing: Song YW, Lee EB.

# INTRODUCTION

Venous thromboembolism (VTE), including pulmonary thromboembolism (PTE) and deep vein thrombosis (DVT), is a global public health problem, and its prevalence is increasing steadily.[1] A substantial proportion of individuals with VTE go unrecognized; these untreated patients experience high mortality and morbidity.[2] However, timely diagnosis is difficult because the initial symptoms of VTE are varied and nonspecific.[3] Although several radiologic tests are useful for diagnosing VTE, they are not appropriate for screening due to limited availability, high cost, and safety issues.[4,5]

The plasma D-dimer test, which is performed easily in an outpatient clinic, is used to screen for VTE. The D-dimer test detects a degradation product of cross-linked fibrin, which is an essential component of a thrombus.[5] A positive D-dimer test result suggests significant thrombus formation and degradation. Previous studies report that the sensitivity and specificity of the test range from 85%–96% and 48%–74%, respectively.[6] Therefore, the D-dimer test is used widely to determine the need for confirmatory radiologic examination.[5] However, the test is nonspecific and D-dimer values may increase in those who are pregnant, have recently undergone surgery, or have cancer, or systemic inflammatory conditions.[7,8]

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by damage to multiple organs caused by autoantibodies and immune complexes.[9] Among autoimmune diseases, SLE conveys the greatest overall risk of VTE (3–4-fold higher than for the general population), which is caused by common occurrence of anti-phospholid (APL) antibody.[10] Therefore, prompt detection of VTE in patients with SLE is highly important. However, the D-dimer test may not work well for SLE because D-dimer levels can vary depending on the degree of inflammation.[11] Therefore, the present study aimed to assess the utility of the D-dimer test as a screening tool for VTE in SLE patients.

# METHODS

### Study subjects

The catchment population comprised patients who underwent D-dimer testing at Seoul National University Hospital between January 2000 and July 2017. The SLE group comprised patients diagnosed with SLE according to the classification criteria revised by the American College of Rheumatology in 1997.[12] After excluding patients with common rheumatologic diseases (antiphospholipid syndrome, inflammatory myositis, rheumatoid arthritis, mixed connective tissue disease, SLE, Sjögren's syndrome, systemic sclerosis, Behcet's disease and vasculitis), control subjects were randomly selected. Wells scores were calculated retrospectively from the selected SLE and control subjects, and then, we divided into "VTE unlikely" and "likely" group according to Well's criteria predicting probability of VTE.[13,14] "VTE likely" patients were excluded since imaging study should be performed immediately without D-dimer test in these patients. After exclusion, a total of 276 SLE patients were enrolled. Among the control group, 4-fold age, and sex matched subjects (n = 1,104) were selected.

### Data collection

All data were retrieved from electronic medical records held at Seoul National University Hospital. Demographic data, including age, sex, body mass index (BMI), previous history of VTE, major surgery within the previous 12 weeks, and comorbidities were collected.

Comorbidities were categorized according to the presence of the following conditions: malignancy (receiving treatment for cancer [currently or within the previous 6 months]), hypertension (HTN), cardiovascular disease (CVD; heart failure, ischemic heart disease or coronary artery occlusive disease), atrial fibrillation, dyslipidemia, diabetes mellitus (DM), cerebral infarction, chronic kidney disease (CKD [epidermal growth factor receptor < 60 mL/min/1.73 m$^2$]), pulmonary artery hypertension (PAH), interstitial lung disease (ILD), other lung diseases (chronic obstructive lung disease, pulmonary tuberculosis, bronchiectasis), or liver cirrhosis. We also collected the following biochemical laboratory data including white blood cell (WBC), hemoglobin, platelet, cholesterol, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen, prothrombin time (PT), activated partial thromboplastin time (aPTT), lupus anticoagulant (LA), and other APL antibodies (anti-β2 glycoprotein I [anti-β2 GP I] antibody or anti-cardiolipin [aCL] antibody). The D-dimer test was performed by an immunoturbidimetric assay using the ACL 3000 (Beckman Coulter Inc., Fullerton, CA, USA).[15] The cut-off value for positivity of D-dimer was defined as a 500 ng/mL previously reported.[16] The SLE disease activity index 2000 (SLEDAI-2K) was calculated.[17] The presence of VTE (PTE and/or DVT) was confirmed by imaging tests, which include pulmonary computed tomography angiography, lung perfusion scans, and duplex ultrasonography.

### Statistical analysis

Continuous variables were expressed as the mean ± standard deviation (SD) or as the median (interquartile range, IQR), while categorical variables were expressed as a number (%). The $\chi^2$ test was used to compare the categorical data between SLE patients and matched control subjects. The Kolmogorov-Smirnov test was performed to determine the normality of the distribution of parameters. Continuous values were compared using the Student's $t$-test or Mann–Whitney $U$ test. The sensitivity, specificity, and positive and negative predictive values (PPV and NPV) of the D-dimer test was calculated for both groups. Receiver operating curve (ROC) analysis was performed to examine the utility of the D-dimer test as a screening tool for VTE for both groups. To examine the relationship between D-dimer levels and clinical parameters in SLE patients, multiple linear regression analyses of D-dimer levels was also conducted. Selection of covariables was performed by the stepwise method. Variables that had a $P$ value of < 0.1 on univariate analysis were selected for multivariate analysis. Finally, to define a subgroup of SLE patients in whom D-dimer test is useful, area under the curves (AUC) were calculated from the ROC curves constructed for different subgroups. All statistical analyses were performed using SPSS (version 23.0; IBM Co., Armonk, NY, USA). $P$ values less than 0.05 were considered significant.

### Ethics statement

The study was approved by the Institutional Review Board (IRB) of Seoul National University Hospital. The need for informed consent was waived by the IRB due to the retrospective nature of the study (IRB protocol No. H-1708-093-878).

## RESULTS

### Baseline characteristics of SLE patients and matched control subjects

The baseline characteristics of SLE patients (n = 276) and matched control subjects (n = 1,104) are shown in **Table 1**. The mean ± SD age of SLE patients was 36.7 ± 13.6 years and that of controls was 38.0 ± 12.6 years. Comorbidities, including HTN, CVD, dyslipidemia, DM, cerebral infarction, CKD, PAH, and ILD were more prevalent in the SLE group than in the control

**Table 1.** Baseline characteristics of the study subjects

| Characteristics | SLE (n = 276) | Controls (n = 1,104) |
|---|---|---|
| Age, yr | 36.7 ± 13.6 | 38.0 ± 12.6 |
| Female | 241 (87.3) | 932 (84.4) |
| Disease duration, yr | 8.4 ± 5.6 | |
| BMI, kg/m$^2$ | 22.8 ± 4.7 | 23.7 ± 10.8 |
| Thrombosis event | 30 (10.9) | 44 (4.0) |
|   PTE | 11 (4.0) | 24 (2.2) |
|   DVT | 16 (5.8) | 13 (1.2) |
|   Both | 3 (1.1) | 7 (0.6) |
|   Previous diagnosed VTE | 8 (2.9) | 15 (1.4) |
| Major surgery within the previous 12 wk | 7 (2.5) | 54 (4.9) |
| Comorbidity | | |
|   Malignancy | 9 (3.3) | 92 (8.3) |
|   HTN | 93 (33.7) | 72 (6.5) |
|   CVD | 28 (10.1) | 45 (4.1) |
|   Atrial fibrillation | 6 (2.2) | 22 (2.0) |
|   Dyslipidemia | 28 (10.1) | 32 (2.9) |
|   DM | 35 (12.7) | 35 (3.2) |
|   Cerebral infarction | 29 (10.5) | 36 (3.3) |
|   CKD, eGFR < 60 mL/min/1.73 cm$^2$ | 43 (15.6) | 30 (2.7) |
|   PAH | 42 (15.2) | 8 (0.7) |
|   ILD | 24 (8.7) | 5 (0.5) |
|   Other lung disease | 7 (2.5) | 10 (0.9) |
|   Liver cirrhosis | 4 (1.4) | 8 (0.7) |
| D-dimer positivity, ≥ 500 ng/mL | 204 (73.9) | 201 (18.2) |
| Laboratory findings | | |
|   ESR, mm/hr | 30.5 (16.0–57.3) | 15.0 (7.0–30.0) |
|   CRP, mg/dL | 0.7 (0.2–4.5) | 0.08 (0.02–0.4) |
|   WBC, /μL | 6,330.0 (4,300.0–9,645.0) | 6,690.0 (5,335.0–8,525.0) |
|   Hemoglobin, g/dL | 10.9 ± 2.2 | 13.0 ± 5.0 |
|   Platelet, × 10$^3$/μL | 178.8 ± 101.4 | 251.0 ± 83.3 |
|   Cholesterol, mg/dL | 172.1 ± 59.9 | 184.4 ± 40.5 |
|   D-dimer, ng/mL | 950.0 (465.0–2,300.0) | 200.0 (110.0–380.0) |
|   PT, INR | 1.1 ± 0.3 | 1.1 ± 0.3 |
|   aPTT, sec | 38.8 ± 16.1 | 32.7 ± 6.7 |
|   Fibrinogen, mg/dL | 345.0 (281.0–440.8) | 301.0 (257.0–366.0) |

Results are expressed as the mean ± standard deviation, as the median (interquartile range), or as number (%).
SLE = systemic lupus erythematosus, BMI = body mass index, PTE = pulmonary thromboembolism, DVT = deep vein thrombosis, VTE = venous thromboembolism, HTN = hypertension, CVD = cardiovascular disease, DM = diabetes mellitus, CKD = chronic kidney disease, eGFR = epidermal growth factor receptor, PAH = pulmonary artery hypertension, ILD = interstitial lung disease, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, WBC = white blood cell, PT = prothrombin time, INR = international normalized ratio, aPTT = activated partial thromboplastin time.

group. ESR, CRP, aPTT and fibrinogen levels were higher in the SLE group than in the control group, whereas hemoglobin and platelet counts were lower in the SLE group than in the control group. The median D-dimer levels were higher in the SLE group than in the control group (950 [465.0–2300.0] vs. 200 [110.0–380.0]). Accordingly, D-dimer positivity (≥ 500 ng/mL) was more common in SLE patients than in control subjects (73.9% vs. 18.2%, respectively).

### Venous thromboembolisms in SLE and control groups
The incidence of VTE was higher in SLE patients than in controls (30/276, 10.9% *vs.* 44/1,104, 4.0%). There were 11 (4.0%) cases of PTE, 16 (5.8%) of DVT, and three concomitant case (1.1%) of PTE and DVT in the SLE patient group, compared with 24 (2.2%) PTE, 13 (1.2%) DVT, and 7 (0.6%) of both PTE and DVT cases in the control group (**Table 1**).
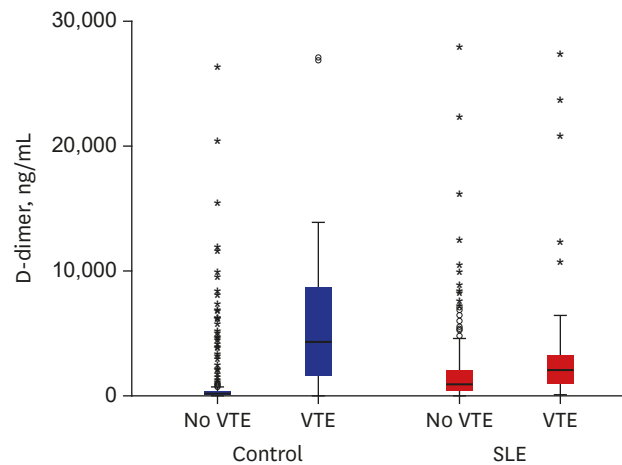
**Fig. 1.** D-dimer levels in SLE and control subjects according to the presence of VTE.
D-dimer levels were highly discriminative between VTE and no VTE group in control subjects. On the contrary, D-dimer levels were comparable between the two groups in SLE patients.
SLE = systemic lupus erythematosus, VTE = venous thromboembolism.

## Low specificity of the D-dimer test as a screening tool for VTE in SLE patients

We compared D-dimer levels between SLE patients and controls with/without VTE. While D-dimer levels were similar in SLE patients with and without VTE, those were significantly different in controls (**Fig. 1**). We found that 204 (73.9%) of 276 SLE patients had a D-dimer level greater than the cut-off value of 500 ng/mL; of these, only 28 (13.7%) had confirmed VTE. Meanwhile, only 201 (18.2%) of 1,104 control subjects showed D-dimer more than 500 ng/mL and 40 patients (19.9%) among them were confirmed VTE. The sensitivity, specificity, PPV, and NPV of the D-dimer test for VTE in SLE patients were 93.3%, 28.4%, 13.7%, and 97.2%, respectively, compared with 90.9%, 84.8%, 19.9%, and 99.5%, respectively, in the controls (**Table 2**). ROC analysis for the D-dimer levels revealed that an AUC was 0.900 (95% confidence interval [95% CI], 0.836–0.963) for control subjects (**Fig. 2A**), but an AUC was only 0.669 (95% CI, 0.575–0.763) for SLE subjects (**Fig. 2B**). These findings suggest that D-dimer test for VTE was much less specific in SLE patients than in controls.

## Clinical variables related to D-dimer levels in controls and SLE patients

Next, we evaluated the clinical factors affecting D-dimer levels in study subjects. Control subjects with a positive D-dimer test greater than 500 ng/mL were significantly older, had more comorbidities (including malignancy, HTN, CVD, atrial fibrillation, DM, CKD, PAH, and ILD) and showed higher levels of coagulation factors (including PT, aPTT, and fibrinogen) than those with negative D-dimer result. However, there was no significant difference in comorbidities (except CVD and DM) and levels of coagulation factors between SLE patients with positive and negative D-dimer test (**Table 3**).

**Table 2.** Diagnostic utility of the D-dimer test in the SLE and control groups[a]

| Variables | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| SLE | 28/30 (93.3) | 70/246 (28.4) | 28/204 (13.7) | 70/72 (97.2) |
| Control | 40/44 (90.9) | 899/1,060 (84.8) | 40/201 (19.9) | 899/903 (99.5) |

Results are expressed as number (%).
SLE = systemic lupus erythematosus, PPV = positive predictive value, NPV = negative predictive value.
[a]Cut-off value, 500 ng/mL.
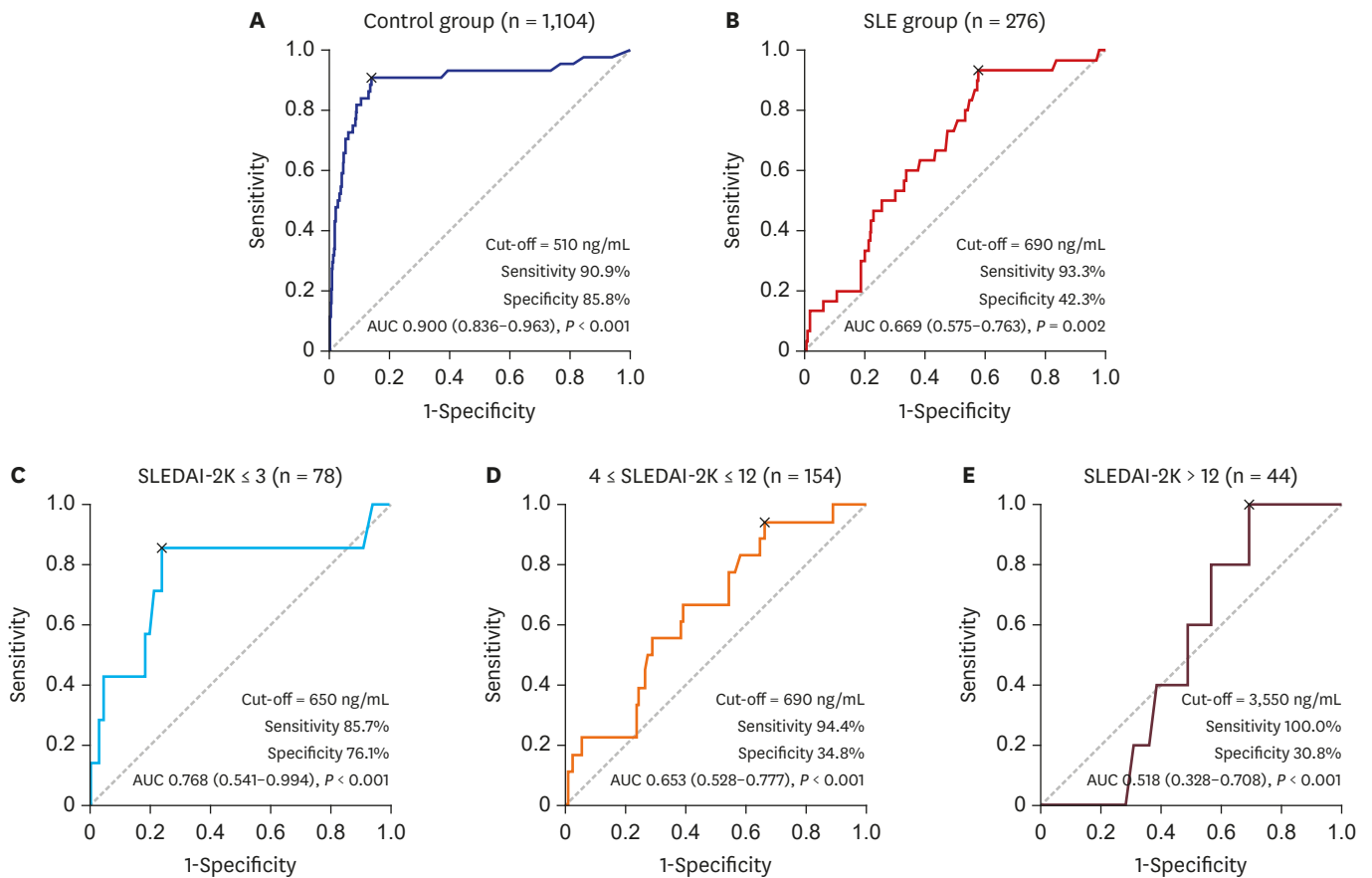
**Fig. 2.** ROC curves of D-dimer for VTE in study subjects.
On ROC curve analysis, (A) the AUC for predicting VTE was 0.900 (95% CI, 0.836–0.963) in control subjects, (B) 0.669 (95% CI, 0.575–0.763) in SLE subjects. When SLE patients were subdivided according to SLEDAI-2K, the AUC for the D-dimer in SLEDAI-2K ≤ 3 was (C) 0.768 (95% CI, 0.541–0.994), (D) 0.653 (95% CI, 0.528–0.777) in 4 ≤ SLEDAI-2K ≤ 12, (E) 0.518 (95% CI, 0.328–0.708) in SLEDAI-2K > 12.
ROC = receiver operating curve, VTE = venous thromboembolism, AUC = area under the curve, CI = confidence interval, SLE = systemic lupus erythematosus, SLEDAI-2K = SLE disease activity index-2000.

In SLE patients, anti-double stranded DNA antibody (anti-dsDNA Ab) titers, urine protein to creatinine ratio (UPCR), and SLEDAI-2K scores reflecting SLE disease activity were significantly higher in patients with a positive D-dimer result than those with a negative result. In addition, complement (C) 3 and C4 levels were significantly lower in patients with D-dimer levels greater than 500 ng/mL compared to those in patients with low D-dimer levels. Multiple linear regression analysis demonstrated that the SLEDAI-2K (β = 0.155; $P$ = 0.022) was significantly associated with the D-dimer levels besides VTE (β = 0.185; $P$ = 0.003), WBC (β = 0.200; $P$ = 0.002), and platelet (β = −0.207; $P$ = 0.002) in SLE patients (**Table 4**). These findings indicate that D-dimer levels in SLE patients are closely related with disease activity.

### ROC analysis of D-dimer levels in SLE patients according to disease activity

Since D-dimer level is affected by disease activity in SLE patients, we analyzed the effect of disease activity on the utility of D-dimer test for predicting VTE in SLE patients. When SLE patients were subdivided according to SLEDAI-2K, the AUC was 0.768 (95% CI, 0.541–0.994) in no flare patients (SLEDAI-2K ≤ 3) (**Fig. 2C**), 0.653 (95% CI, 0.528–0.777) in patients

**Table 3.** Variables affecting D-dimer values in the SLE group and control group

| Variables | SLE (n = 276) | | | Control (n = 1,104) | | |
|---|---|---|---|---|---|---|
| | High[a] (n = 204) | Normal[b] (n = 72) | P value | High[a] (n = 201) | Normal[b] (n = 903) | P value |
| Age, yr | 37.0 ± 14.0 | 35.8 ± 12.3 | 0.534 | 41.2 ± 13.8 | 37.4 ± 12.2 | < 0.001 |
| Female | 175 (85.8) | 66 (91.7) | 0.223 | 176 (87.6) | 756 (83.7) | 0.197 |
| BMI, kg/m² | 22.97 ± 4.6 | 22.2 ± 5.1 | 0.322 | 24.8 ± 16.4 | 23.3 ± 8.1 | 0.258 |
| Thrombosis event | 28 (13.7) | 2 (2.8) | 0.008 | 40 (19.9) | 4 (0.4) | < 0.001 |
| PTE | 11 (5.4) | 0 (0.0) | | 22 (10.9) | 2 (0.2) | |
| DVT | 14 (6.8) | 2 (2.8) | | 11 (5.5) | 2 (0.2) | |
| Both | 3 (1.5) | 0 (0.0) | | 7 (3.5) | 0 (0.0) | |
| Major surgery within the previous 12 wk | 5 (2.5) | 2 (2.8) | 1.000 | 13 (6.5) | 41 (4.5) | 0.277 |
| Comorbidity | | | | | | |
| Malignancy | 7 (3.4) | 2 (2.8) | 1.000 | 38 (18.9) | 54 (6.0) | < 0.001 |
| HTN | 72 (35.3) | 21 (29.2) | 0.386 | 20 (10.0) | 52 (5.8) | 0.039 |
| CVD | 11 (5.4) | 17 (23.6) | < 0.001 | 17 (8.5) | 28 (3.1) | 0.001 |
| Atrial fibrillation | 6 (2.9) | 0 (0.0) | 0.345 | 10 (5.0) | 12 (1.3) | 0.004 |
| Dyslipidemia | 22 (10.8) | 6 (8.3) | 0.654 | 6 (3.0) | 26 (2.9) | 1.000 |
| DM | 31 (15.2) | 4 (5.6) | 0.039 | 13 (6.5) | 22 (2.4) | 0.006 |
| Cerebral infarction | 19 (9.3) | 10 (13.9) | 0.272 | 11 (5.5) | 25 (2.8) | 0.075 |
| CKD, eGFR < 60 mL/min/1.73 cm² | 37 (18.1) | 6 (8.3) | 0.058 | 15 (7.5) | 15 (1.7) | < 0.001 |
| PAH | 35 (17.1) | 7 (9.7) | 0.412 | 4 (2.0) | 4 (0.4) | 0.041 |
| ILD | 22 (10.8) | 2 (2.8) | 0.117 | 3 (1.5) | 2 (0.2) | 0.045 |
| Other lung disease | 7 (3.4) | 0 (0.0) | 0.196 | 4 (2.0) | 6 (0.7) | 0.091 |
| Liver cirrhosis | 4 (2.0) | 0 (0.0) | 0.576 | 1 (0.5) | 7 (0.8) | 1.000 |
| Antiphospholipid syndrome | 10 (4.9) | 9 (12.5) | 0.053 | - | - | - |
| SLEDAI-2K | 8.3 ± 5.2 | 3.0 ± 3.4 | < 0.001 | - | - | - |
| Laboratory findings | | | | | | |
| ESR, mm/hr | 34.0 (17.0–60.5) | 28.0 (15.5–46.3) | 0.171 | 24.0 (11.3–42.5) | 14.0 (6.0–27.0) | 0.001 |
| CRP, mg/dL | 1.3 (0.2–5.3) | 0.2 (0.0–0.6) | < 0.001 | 0.8 (0.1–4.3) | 0.1 (0.0–0.2) | < 0.001 |
| WBC, /μL | 6,605.0 (4,317.5–9,770.0) | 6,120.0 (4,292.5–8,757.5) | 0.426 | 6,985.0 (5,300.0–10,257.5) | 6,610.0 (5,340.0–8,300.0) | 0.020 |
| Hemoglobin, g/dL | 10.5 ± 2.1 | 12.1 ± 2.0 | < 0.001 | 11.9 ± 7.7 | 13.3 ± 4.2 | 0.020 |
| Platelet, × 10³/μL | 164.2 ± 100.9 | 220.4 ± 91.4 | < 0.001 | 236.4 ± 114.0 | 254.3 ± 74.5 | 0.035 |
| Cholesterol, mg/dL | 169.9 ± 63.7 | 178.2 ± 47.6 | 0.248 | 180.7 ± 52.4 | 185.3 ± 37.4 | 0.247 |
| D-dimer, ng/mL | 1,540.0 (860.0–3,305.0) | 225.0 (162.5–337.5) | < 0.001 | 1,510.0 (670–4,215.0) | 160.0 (100–250) | < 0.001 |
| PT, INR | 1.1 ± 0.3 | 1.0 ± 0.4 | 0.404 | 1.2 ± 0.6 | 1.0 ± 0.2 | 0.001 |
| aPTT, sec | 39.2 ± 16.9 | 37.5 ± 13.4 | 0.451 | 34.1 ± 11.3 | 32.4 ± 5.1 | 0.049 |
| Fibrinogen, mg/dL | 360.0 (276.0–469.0) | 328.0 (285.0–395.0) | 0.134 | 372.0 (274.0–460.0) | 294.0 (254.0–348.0) | < 0.001 |
| Lupus anticoagulant | 64/191 (33.5) | 18/64 (28.1) | 0.445 | - | - | - |
| Anti-β2GP I Ab or aCL Ab | 56/186 (30.1) | 17/59 (28.8) | 1.000 | - | - | - |
| Complement 3, mg/dL | 72.0 ± 37.8 | 91.5 ± 26.6 | < 0.001 | - | - | - |
| Complement 4, mg/dL | 13.1 ± 9.8 | 16.5 ± 6.4 | 0.001 | - | - | - |
| Anti-ds DNA Ab, IU/mL | 162.3 ± 603.0 | 32.9 ± 104.8 | 0.004 | - | - | - |
| UPCR, mg/g | 2.3 ± 3.9 | 0.5 ± 1.1 | < 0.001 | - | - | - |

Results are expressed as the mean ± standard deviation, as the median (interquartile range), or as number (%).
SLE = systemic lupus erythematosus, BMI = body mass index, PTE = pulmonary thromboembolism, DVT = deep vein thrombosis, HTN = hypertension, CVD = cardiovascular disease, DM = diabetes mellitus, CKD = chronic kidney disease, eGFR = epidermal growth factor receptor, PAH = pulmonary artery hypertension, ILD = interstitial lung disease, SLEDAI-2K = systemic lupus erythematosus disease activity index 2000, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, WBC = white blood cell, PT = prothrombin time, INR = international normalized ratio, aPTT = activated partial thromboplastin time, anti β2GP I Ab = anti-β2 glycoprotein I antibody, aCL Ab = anti-cardiolipin antibody, anti-dsDNA Ab = anti-double-stranded DNA antibody, UPCR = urine protein to creatinine ratio.
[a]High, D-dimer ≥ 500 ng/mL; [b]Normal, D-dimer < 500 ng/mL.

with mild to moderate flare (4 ≤ SLEDAI-2K ≤ 12) (**Fig. 2D**), 0.518 (95% CI, 0.328–0.708) in patients with high SLEDAI-2K (SLEDAI-2K > 12) (**Fig. 2E**). These findings demonstrated that in SLE patients with high disease activity (SLEDAI-2K > 12), D-dimer was less capable of predicting VTE than in those with low disease activity (SLEDAI-2K ≤ 3).

**Table 4.** Multivariate linear regression analysis of factors affecting D-dimer levels in the SLE and control groups

| Variables | SLE (n = 276) | | | | Control (n = 1,104) | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate | | Multivariate | | Univariate | | Multivariate | |
| | β | P value | β | P value | β | P value | β | P value |
| Age, yr | 0.027 | 0.661 | - | - | 0.086 | 0.004 | 0.005 | 0.887 |
| BMI, kg/m² | −0.115 | 0.076 | −0.081 | 0.188 | 0.020 | 0.702 | - | - |
| VTE | 0.171 | 0.004 | 0.185 | 0.003 | 0.401 | < 0.001 | 0.316 | < 0.001 |
| CRP, mg/dL | 0.160 | 0.008 | 0.008 | 0.898 | 0.237 | < 0.001 | 0.106 | 0.004 |
| WBC | 0.227 | < 0.001 | 0.200 | 0.002 | 0.068 | 0.024 | 0.046 | 0.158 |
| Hemoglobin, g/dL | −0.124 | 0.040 | −0.013 | 0.843 | −0.056 | 0.063 | < 0.001 | 0.997 |
| Platelet, × 10³/μL | −0.220 | < 0.001 | −0.207 | 0.002 | −0.066 | 0.028 | −0.044 | 0.181 |
| PT, INR | 0.099 | 0.102 | - | - | 0.115 | < 0.001 | −0.006 | 0.869 |
| aPTT, sec | −0.085 | 0.163 | - | - | 0.111 | < 0.001 | 0.045 | 0.182 |
| Fibrinogen, mg/dL | 0.028 | 0.653 | - | - | 0.088 | 0.006 | 0.028 | 0.424 |
| SLEDAI-2K | 0.221 | < 0.001 | 0.155 | 0.022 | - | - | - | - |

SLE = systemic lupus erythematosus, BMI = body mass index, VTE = venous thromboembolism, CRP = C-reactive protein, WBC = white blood cell, PT = prothrombin time, INR = international normalized ratio, aPTT = activated partial thromboplastin time, SLEDAI-2K = systemic lupus erythematosus disease activity index 2000.

## DISCUSSION

This is a case-control study to evaluate the role of D-dimer in predicting VTE in SLE patients. The results presented herein suggest that D-dimer test may not be a useful tool for the screening of VTE in SLE patients (AUC = 0.669 for the SLE group vs. 0.90 for the control group), because it is difficult to distinguish between true VTE and secondary elevation reflecting inflammation in SLE patients. However, present study also demonstrated that the D-dimer test can be useful for VTE screening in stable SLE patients.

Arterial or venous thromboembolic complications are frequent manifestations of SLE; indeed, 5%–10% of SLE patients have VTE.[18] Incidence of thrombosis has been reported to be up to 51.9 per 1,000 patient-years and the risk is 3–4 fold higher than for the general population.[19] This study showed that VTE was more frequently observed in SLE patients than in the control subjects (10.9% vs. 4.0%). An increased risk of thrombo-embolic complications can be due to the fact that SLE patients often experience a hypercoagulable status including positive APL antibodies, systemic inflammation, or anticoagulation deficiency.[20] Previous reports have shown that inflammatory mediators, which are increased in SLE patients, can increase serum tissue factor levels and inhibit activation of protein C.[21,22] Patients with SLE have a deficiency in natural anticoagulant mechanisms and upregulation of coagulation factors associated with inflammatory mechanisms and endothelial damage.[23] Thus, blood coagulation is easily activated in SLE patients with active inflammation.[24]

The D-dimer test is the standard screening tool for predicting VTE in general population with Wells probability score.[14,25,26] If VTE is 'likely' with Wells criteria, confirmatory imaging tests should be performed immediately, while D-dimer test should be performed to exclude VTE if it is 'unlikely' with Well's criteria.[14,25,27] In this study, we found that the D-dimer levels cannot be clearly delineated between patients with and without VTE in SLE (**Fig. 1**), which lead to very low specificity of D-dimer test in this group. Therefore, if a clinician follows the general algorithm for VTE, then patients may be subjected to unnecessary imaging tests, which are not only costly but can be dangerous because of unnecessary radiation exposure.

False elevation of D-dimer levels can arise from different conditions such as aging, cancer, co-morbidities (including heart failure, chronic obstructive pulmonary disease, and

atherosclerosis), and systemic inflammation.[28-31] In this study, we found that in SLE patients, a positive D-dimer test is closely associated with high SLE disease activity, as reflected by a higher SLEDAI-2K including higher anti-dsDNA titers, low complement levels, and a high UPCR (**Table 3**). Therefore, utility of D-dimer test can be affected by disease activity in SLE patients; AUC value for D-dimer in ROC is high in SLE patients with low SLEDAI-2K, while it is low in patients with high SLEDAI-2K (**Fig. 2C-E**).

Taken together, disease activity should be considered in the interpretation of D-dimer test in SLE patients. In low disease activity, positive D-dimer test result can be regarded as in general population. So, confirmatory imaging test should be performed if D-dimer test is positive in this group of patents. However, D-dimer level can be elevated without association with VTE in SLE patients with high disease activity.

This study has several limitations. First of all, the study is retrospective in design. Therefore, some patients with VTE might have gone undetected because not all enrolled patients underwent imaging studies. However, the result of this study represents the real world situation. In addition, the study population was composed of only Koreans; therefore, the results may not be generalizable to other ethnic groups. Despite these limitations, the insights gained from this study should help clinicians use the D-dimer test more usefully in SLE patients.

In conclusion, our study demonstrated that the D-dimer test may not be useful for screening VTE in SLE patients, especially in those with high disease activity. Therefore, it may be necessary to interpret the result of the D-dimer test in relation to disease activity in patients with SLE.

## REFERENCES

1. Tagalakis V, Patenaude V, Kahn SR, Suissa S. Incidence of and mortality from venous thromboembolism in a real-world population: the Q-VTE Study Cohort. *Am J Med* 2013;126(9):832.e13-21.
   **PUBMED** | **CROSSREF**

2. Stein PD, Matta F. Epidemiology and incidence: the scope of the problem and risk factors for development of venous thromboembolism. *Clin Chest Med* 2010;31(4):611-28.
   **PUBMED** | **CROSSREF**

3. Righini M, Robert-Ebadi H, Le Gal G. Diagnosis of acute pulmonary embolism. *J Thromb Haemost* 2017;15(7):1251-61.
   **PUBMED** | **CROSSREF**

4. Kline JA. Diagnosis and exclusion of pulmonary embolism. *Thromb Res* 2018;163:207-20.
   **PUBMED** | **CROSSREF**

5. Wells PS, Ihaddadene R, Reilly A, Forgie MA. Diagnosis of venous thromboembolism: 20 years of progress. *Ann Intern Med* 2018;168(2):131-40.
   **PUBMED** | **CROSSREF**

6. Geersing GJ, Janssen KJ, Oudega R, Bax L, Hoes AW, Reitsma JB, et al. Excluding venous thromboembolism using point of care D-dimer tests in outpatients: a diagnostic meta-analysis. *BMJ* 2009;339:b2990.
   **PUBMED** | **CROSSREF**

7. Kabrhel C, Mark Courtney D, Camargo CA Jr, Plewa MC, Nordenholz KE, Moore CL, et al. Factors associated with positive D-dimer results in patients evaluated for pulmonary embolism. *Acad Emerg Med* 2010;17(6):589-97.
   **PUBMED** | **CROSSREF**

8. Lee S, Hwang JI, Kim Y, Yoon PW, Ahn J, Yoo JJ. Venous thromboembolism following hip and knee replacement arthroplasty in Korea: a nationwide study based on claims registry. *J Korean Med Sci* 2016;31(1):80-8.
   **PUBMED** | **CROSSREF**

9. Hartman EA, van Royen-Kerkhof A, Jacobs JW, Welsing PM, Fritsch-Stork RD. Performance of the 2012 Systemic Lupus International Collaborating Clinics classification criteria versus the 1997 American College of Rheumatology classification criteria in adult and juvenile systemic lupus erythematosus. A systematic review and meta-analysis. *Autoimmun Rev* 2018;17(3):316-22.
**PUBMED** | **CROSSREF**

10. Aviña-Zubieta JA, Vostretsova K, De Vera MA, Sayre EC, Choi HK. The risk of pulmonary embolism and deep venous thrombosis in systemic lupus erythematosus: a general population-based study. *Semin Arthritis Rheum* 2015;45(2):195-201.
**PUBMED** | **CROSSREF**

11. Linkins LA, Takach Lapner S. Review of D-dimer testing: good, bad, and ugly. *Int J Lab Hematol* 2017; 39 Suppl 1:98-103.
**PUBMED** | **CROSSREF**

12. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40(9):1725.
**PUBMED** | **CROSSREF**

13. Geersing GJ, Zuithoff NP, Kearon C, Anderson DR, Ten Cate-Hoek AJ, Elf JL, et al. Exclusion of deep vein thrombosis using the Wells rule in clinically important subgroups: individual patient data meta-analysis. *BMJ* 2014;348:g1340.
**PUBMED** | **CROSSREF**

14. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. *Lancet* 2012;379(9828):1835-46.
**PUBMED** | **CROSSREF**

15. Lee YS, Lee YK, Han SB, Nam CH, Parvizi J, Koo KH. Natural progress of D-dimer following total joint arthroplasty: a baseline for the diagnosis of the early postoperative infection. *J Orthop Surg* 2018;13(1):36.
**PUBMED** | **CROSSREF**

16. Righini M, Nendaz M, Le Gal G, Bounameaux H, Perrier A. Influence of age on the cost-effectiveness of diagnostic strategies for suspected pulmonary embolism. *J Thromb Haemost* 2007;5(9):1869-77.
**PUBMED** | **CROSSREF**

17. Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002;29(2):288-91.
**PUBMED**

18. Mok CC, Ho LY, Yu KL, To CH. Venous thromboembolism in southern Chinese patients with systemic lupus erythematosus. *Clin Rheumatol* 2010;29(6):599-604.
**PUBMED** | **CROSSREF**

19. Sarabi ZS, Chang E, Bobba R, Ibanez D, Gladman D, Urowitz M, et al. Incidence rates of arterial and venous thrombosis after diagnosis of systemic lupus erythematosus. *Arthritis Rheum* 2005;53(4):609-12.
**PUBMED** | **CROSSREF**

20. Zaldívar-Alcántara H, Herrera-Jiménez LE, Dehesa-López E, Correa-Rotter R. Risk factors for the development of thrombotic complication in patients with lupus erythematosus and lupus nephropatic. *Rev Invest Clin* 2013;65(3):199-208.
**PUBMED**

21. Xu J, Lupu F, Esmon CT. Inflammation, innate immunity and blood coagulation. *Hamostaseologie* 2010;30(1):5-6, 8-9.
**PUBMED** | **CROSSREF**

22. Lundström E, Gustafsson JT, Jönsen A, Leonard D, Zickert A, Elvin K, et al. HLA-DRB1*04/*13 alleles are associated with vascular disease and antiphospholipid antibodies in systemic lupus erythematosus. *Ann Rheum Dis* 2013;72(6):1018-25.
**PUBMED** | **CROSSREF**

23. Dhillon PK, Adams MJ. Thrombosis in systemic lupus erythematosus: role of impaired fibrinolysis. *Semin Thromb Hemost* 2013;39(4):434-40.
**PUBMED** | **CROSSREF**

24. Meesters EW, Hansen H, Spronk HM, Hamulyak K, Rosing J, Rowshani AT, et al. The inflammation and coagulation cross-talk in patients with systemic lupus erythematosus. *Blood Coagul Fibrinolysis* 2007;18(1):21-8.
**PUBMED** | **CROSSREF**

25. Wells PS, Anderson DR, Rodger M, Ginsberg JS, Kearon C, Gent M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost* 2000;83(3):416-20.
**PUBMED** | **CROSSREF**

26. Wells PS, Owen C, Doucette S, Fergusson D, Tran H. Does this patient have deep vein thrombosis? *JAMA* 2006;295(2):199-207.
    **PUBMED | CROSSREF**

27. Park R, Seo YI, Yoon SG, Choi TY, Shin JW, Uh ST, et al. Utility of D-dimer assay for diagnosing pulmonary embolism: single institute study. *Korean J Lab Med* 2008;28(6):419-24.
    **PUBMED | CROSSREF**

28. Kim JY, Kim KH, Cho JY, Sim DS, Yoon HJ, Yoon NS, et al. D-dimer/troponin ratio in the differential diagnosis of acute pulmonary embolism from non-ST elevation myocardial infarction. *Korean J Intern Med* 2019;34(6):1263-71.
    **PUBMED | CROSSREF**

29. Kim SA, Yhim HY, Bang SM. Current management of cancer-associated venous thromboembolism: focus on direct oral anticoagulants. *J Korean Med Sci* 2019;34(6):e52.
    **PUBMED | CROSSREF**

30. Lozano-Polo L, Puig-Campmany M, Herrera-Mateo S, Mateo-Roca M, Santos-Rodríguez JA, Benito-Vales S. Diagnosis of pulmonary embolism in the elderly: adherence to guidelines and age-adjusted D-dimer concentration values. *Emergencias* 2018;30(5):321-7.
    **PUBMED**

31. Alvarez-Perez FJ, Castelo-Branco M, Alvarez-Sabin J. Usefulness of measurement of fibrinogen, D-dimer, D-dimer/fibrinogen ratio, C reactive protein and erythrocyte sedimentation rate to assess the pathophysiology and mechanism of ischaemic stroke. *J Neurol Neurosurg Psychiatry* 2011;82(9):986-92.
    **PUBMED | CROSSREF**