# Diagnostic accuracy of deep vein thrombosis is increased by analysis using combined optimal cut-off values of postoperative plasma D-dimer levels

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**Abstract.** The present study aimed to evaluate the accuracy of analysis using optimal cut-off values of plasma D-dimer levels in the diagnosis of deep vein thrombosis (DVT). A total of 175 orthopedic patients with DVT and 162 patients without DVT were included in the study. Ultrasonic color Doppler imaging was performed on lower limb veins prior to and following orthopedic surgery in order to determine the types of orthopedic conditions that were present. An enzyme-linked fluorescent assay was performed to detect the expression levels of D-dimer in plasma, and receiver operating characteristic analysis was performed to predict the occurrence of DVT on the basis of the expression levels of D-dimer. After surgery, the expression levels of D-dimer in the plasma of DVT patients were significantly higher in comparison with those in orthopedic patients without DVT ($P<0.05$). When the patients were divided into subgroups according to the underlying orthopedic condition, the expression levels of D-dimer in the plasma of each subgroup were higher 1 day after orthopedic surgery in comparison to those prior to surgery ($P<0.05$). The diagnostic accuracy achieved using combined optimal cut-off values at 1 and 3 days post-surgery was significantly higher than the accuracy when using a single optimal cut-off value ($P<0.05$). In conclusion, detection of D-dimer expression levels at 1 day post-orthopedic surgery may be important in predicting DVT. In addition, the diagnostic accuracy of DVT is significantly increased by analysis using combined optimal cut-off values of D-dimer plasma expression levels.

## Introduction

Deep vein thrombosis (DVT) is the formation of a thrombus within a deep vein, predominantly occurring in the legs (1). DVT commonly occurs in 40-80% of patients undergoing orthopedic surgery, such as total hip replacement, total knee replacement and hip fracture surgery (2-4). Pulmonary embolisms can be caused by a detached thrombus that travels to the lungs, and they are a potentially life-threatening complication of DVT with a high mortality rate (5,6). DVT is difficult to diagnosis as patients with DVT often lack clear signs prior to its onset (7-9).

To date, lower limb phlebography has been considered to be the gold standard for the diagnosis of DVT; however, as it is an invasive and high-cost procedure, the application of lower limb phlebography in the diagnosis of liver DVT is limited (10). Color and spectral Doppler ultrasonography is commonly used in the diagnosis of DVT in lower limb veins; however, ultrasonography requires that patients move continually, which can increase patient suffering and is a time-consuming process. On the basis of the above factors, a simple and rapid method of diagnosing DVT is urgently required.

D-dimer is a fibrin degradation product that exists in the blood after a thrombus is degraded by thrombin, coagulation factor XIIIa and fibrinolysin. Expression levels of D-dimer can reflect the activity of coagulation and the fibrinolytic system and, therefore, may be used to diagnose DVT (11,12). Previous studies have demonstrated that expression levels of D-dimer in serum are significantly increased following DVT (13,14). However, the expression levels of D-dimer are also increased when the coagulation and fibrinolysis system is activated in surgery, trauma, bleeding disorders, inflammatory diseases, kidney disease and pregnancy (15). A method of predicting the occurrence of DVT with regards to the expression levels of D-dimer prior to and following orthopedic surgery requires clarification.

In the present study, the expression levels of D-dimer in serum were analyzed in patients with DVT prior to and following orthopedic surgery. Receiver operating characteristic (ROC) analysis was performed in order to predict the occurrence of DVT on the basis of the expression levels of D-dimer in plasma.

## Patients and methods

*Patients*. A total of 175 patients (88 males, 87 females; age range, 59-74 years; average age, 66.42 years) with DVT

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*Key words:* orthopedic surgery, deep vein thrombosis, D-dimer

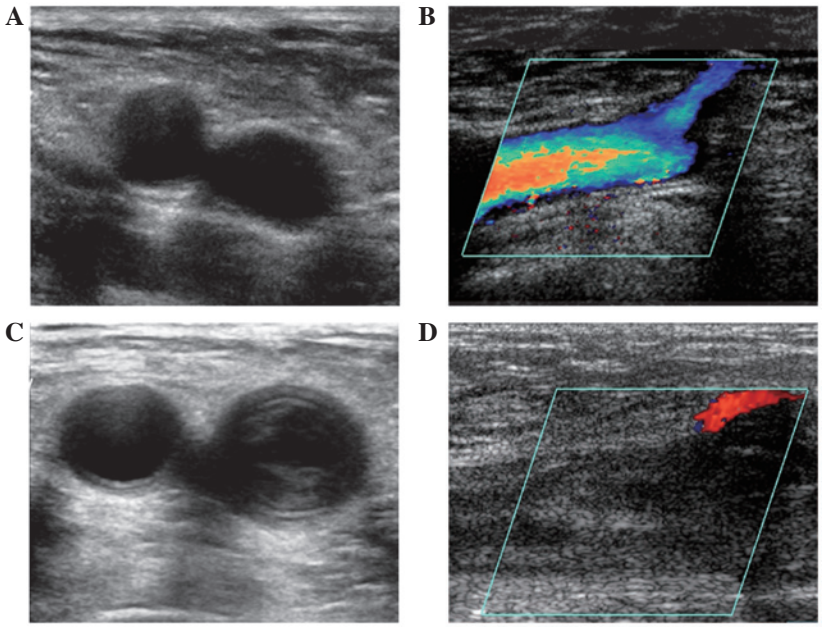


Figure 1. Color Doppler ultrasonography imaging of the deep vein thrombosis (DVT) and non-DVT groups. Color Doppler ultrasonography was performed to detect the size, localization, echogenicity, margins and tendency of the thrombus structure. In the non-DVT group, (A) coronal and (B) axial images revealed that non-significant stenosis occurred in the femoral veins. In the DVT group, (C) coronal and (D) axial images revealed that several thrombi and venous stenosis were present in the femoral veins.

following orthopedic surgery (DVT group) were enrolled in the present study. The prognosis of DVT was founded on clinical manifestations, imaging and laboratory test results. A total of 161 orthopedic patients (56 males, 105 females; age range, 25-86 years; average age, 62.13 years) without DVT following orthopedic surgery (non-DVT group) were included in the present study as control subjects.

The exclusion criteria for the DVT group were as follows: i) Patients with DVT prior to orthopedic surgery; ii) patients with recent active bleeding and spontaneous intracranial hemorrhage; iii) patients with bleeding disorders undergoing anticoagulant treatment; iv) patients with severe liver and kidney disease; v) patients who had not undergone surgery or trauma; vi) patients with history of thrombosis; and vii) patients with malignancies or inflammatory diseases. The study was approved by the Ethics Review Board of the First Affiliated Hospital of Dalian Medical University (Dalian, China) and written informed consent was obtained from every patient.

*Detection of D-dimer expression levels in plasma*. Peripheral venous blood samples were collected from patients prior to orthopedic surgery and at 1, 3 and 7 days after surgery. Blood samples (~1.8 ml) were transferred into anticoagulant tubes (BD Biosciences, San Jose, CA, USA) with 0.2 ml citric acid (109 mM) and mixed. The samples were then centrifuged at 1,700 x g for 15 min. The plasma supernatants were transferred to a new tube for the analysis of D-dimer expression levels. D-dimer was detected using an enzyme-linked fluorescent assay, conducted using a VIDAS D-dimer Exclusion II kit (bioMérieux Inc., Grenoble, France) and a Spectramax M2 microplate reader (Molecular Devices, LCC, Sunnyvale, CA, USA). The detection was performed in accordance with the manufacturer's instructions.

*Color Doppler ultrasonography*. Venous examination of the lower limbs was conducted in patients prior to, and 3 and 7 days after orthopedic surgery. The venous diameter, blood flow, intraluminal pressure, deep venous valve function and thrombosis formation were determined using an ACUSON Antares Color Doppler ultrasound system (Siemens AG, Munich, Germany).

*Statistical analysis*. All results are expressed as the mean ± standard deviation. All statistical analyses were performed using SPSS version 13.0 for Windows (SPSS, Inc., Chicago, IL, USA). A paired t-test was used to analyze the comparisons between groups and the analysis of paired data. ROC analysis was used to determine the ability of D-dimer expression levels to predict DVT. $P<0.05$ was considered to indicate a statistically significant difference.

## Results

*Diagnosis of patients with DVT by color Doppler ultrasonography*. To diagnose DVT, ultrasonic color Doppler imaging was performed on lower limb veins prior to and following orthopedic surgery. Color Doppler ultrasonography provides information regarding the size, localization, echogenicity, margins and tendency of the thrombus structure. As presented in Fig. 1A and B, there was no sign of thrombus in the femoral vein in the non-DVT group, and axial images demonstrated that non-significant stenosis was present in the femoral vein. However, several thrombi were observed in the femoral veins of the non-DVT group, and axial images showed that significant vein stenosis was present (Fig. 1C and D). The underlying conditions of the orthopedic patients with DVT, and the corresponding DVT incidence rates are presented in Table I. The incidence rate of DVT in patients with acetabular dysplasia

Table I. Underlying conditions of orthopedic patients with DVT.

| Condition | Number of patients | Constituent ratio (%) | Incidence of DVT (%) |
|---|---|---|---|
| ANFH | 68 | 39 | 9 |
| OA | 20 | 11 | 10 |
| FNF | 28 | 16 | 11 |
| RA | 19 | 11 | 11 |
| AD | 11 | 6 | 27 |
| CD | 5 | 3 | 0 |
| SF | 24 | 14 | 4 |
| Total | 175 | 100 | 16 |

DVT, deep vein thrombosis; ANFH, osteonecrosis of the femoral head; OA, osteoarthritis; FNF, fractured neck of femur; RA, rheumatoid arthritis; AD, acetabular dysplasia; CD, coxodynia; SF, spinal fracture.

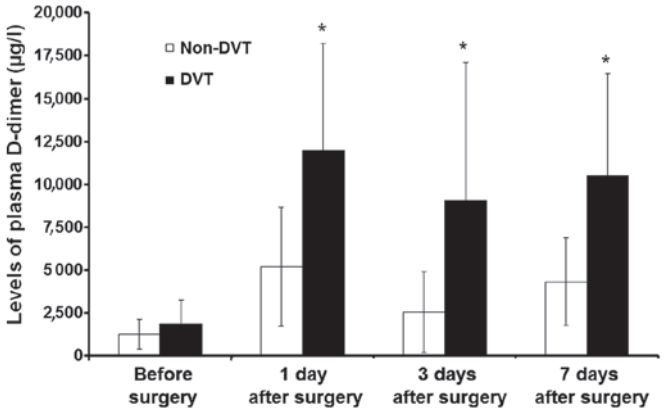


Figure 2. Expression levels of plasma D-dimer in the deep vein thrombosis (DVT) and non-DVT groups detected by an enzyme-linked fluorescent assay 1 day prior to, and 1, 3 and 7 days after orthopedic surgery. Error bars represent the standard error of the mean. *P<0.05 vs. the non-DVT group.

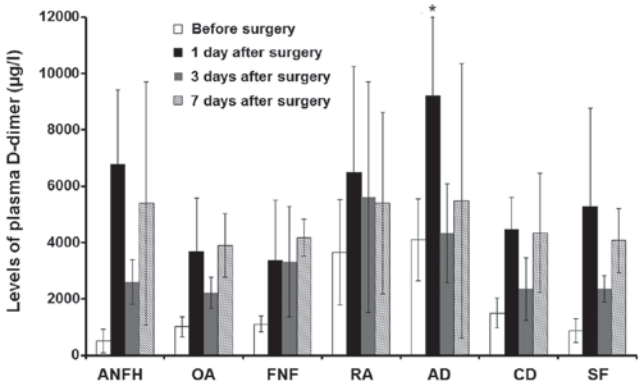


Figure 3. Expression levels of plasma D-dimer in patients with different types of orthopedic disease. Enzyme-linked fluorescent assays were performed to determine plasma D-dimer expression levels in the deep vein thrombosis group prior to, and at 1, 3 and 7 days after orthopedic surgery. Error bars represent the standard error of the mean. *P<0.05 vs. before surgery. ANFH, osteonecrosis of the femoral head; OA, osteoarthritis; FNF, fractured neck of femur; RA, rheumatoid arthritis; AD, acetabular dysplasia; CD, coxodynia; SF, spinal fracture.

was markedly greater compared with that in the patients with other conditions. The incidence of DVT occurring in patients with coxodynia was the lowest of all the conditions listed in Table I.

*Correlation between the expression levels of D-dimer in plasma and the incidence of DVT.* To investigate the correlation between D-dimer and the incidence of DVT, the expression levels of D-dimer in plasma were detected using an enzyme linked fluorescent assay. As presented in Fig. 2, there was no significant difference between the expression levels of D-dimer in plasma between the DVT and the non-DVT group prior to orthopedic surgery. However, at 1 day after orthopedic surgery the expression levels of D-dimer in the plasma of the DVT group were significantly increased in comparison with those in the non-DVT group (P<0.05). Although the expression levels of D-dimer in the plasma decreased slightly on days 3 and 7 following orthopedic surgery, the D-dimer expression levels in the DVT group remained significantly higher than those in the non-DVT group (P<0.05). These results suggest that the expression levels of D-dimer in plasma are correlated with the incidence of DVT.

*Prediction of DVT in patients with different types of orthopedic disease.* To investigate the use of D-dimer expression levels in the prediction of DVT, plasma D-dimer levels were detected in the DVT group at 1 day prior to, and 1, 3 and 7 days after orthopedic surgery. According to the different types of orthopedic condition that required surgery, the DVT group was classified into 7 subgroups (Table I). As presented in Fig. 3, the expression levels of D-dimer in the plasma of each subgroup were higher 1 day after orthopedic surgery in comparison with the expression levels prior to orthopedic surgery (P<0.05). The expression levels of D-dimer in plasma were decreased at 3 days after orthopedic surgery in comparison with the expression levels 1 day after orthopedic surgery, and were increased at 7 days after orthopedic surgery in comparison with 3 days after surgery. Plasma D-dimer expression levels in the fractured neck of femur subgroup were higher at 7 days after orthopedic surgery than at the other time points. With the exclusion of the fractured neck of femur subgroup, plasma D-dimer expression levels in the other 6 subgroups were the highest on day 1 following orthopedic surgery. Plasma D-dimer expression levels in the acetabular dysplasia subgroup were significantly increased in comparison with those in the other subgroups at 1 day after surgery (P<0.05), and this is in accordance with the high incidence of DVT in patients with acetabular dysplasia. These results suggest that the detection of plasma D-dimer expression levels 1 day after orthopedic surgery may be important in the prediction of DVT.

*ROC analysis for predicting DVT using plasma D-dimer expression levels.* To determine the diagnostic accuracy of plasma D-dimer expression levels in predicting the development of DVT in patients with orthopedic disease, ROC analysis was performed. As presented in Fig. 4 and Table II, the area under the ROC curve for plasma D-dimer expression level 1 day after orthopedic surgery in the prediction of DVT

Table II. ROC analysis of the prediction of DVT using plasma D-dimer levels.

| Time point | Area under ROC curve | Standard error | P-value | 95% confidence interval | |
|---|---|---|---|---|---|
| | | | | Lower limit | Upper limit |
| Prior to surgery | 0.660 | 0.048 | 0.011 | 0.666 | 0.854 |
| 1 day after surgery | 0.889 | 0.053 | 0.003 | 0.727 | 0.988 |
| 3 days after surgery | 0.870 | 0.076 | 0.009 | 0.690 | 0.933 |
| 5 days after surgery | 0.732 | 0.087 | 0.004 | 0.626 | 0.967 |

ROC, receiver operating characteristic; DVT, deep vein thrombosis.

was 0.889; the optimal cut-off value was 6,360 $\mu$g/l, and the threshold of the optimal cut-off value had a sensitivity of 92.9% and a specificity of 85%. The area under ROC curve for plasma D-dimer expression level 3 days after orthopedic surgery in the prediction of DVT was 0.870; the optimal cut-off value was 4,580 $\mu$g/l, and the threshold of the optimal cut-off value had a sensitivity of 76.9% and a specificity of 67%. These results indicate that the detection of plasma D-dimer expression levels 1 day after orthopedic surgery is important in the prediction of DVT.

*Combination analysis for predicting DVT using optimal cut-off values of plasma D-dimer expression levels*. To improve the diagnostic accuracy of predicting DVT, combination analysis was performed using plasma D-dimer expression levels at 1 and 3 days after orthopedic surgery. Diagnostic accuracy for predicting DVT is presented in Fig. 5. The diagnostic accuracy predicted using the optimal cut-off value at 1 day after orthopedic surgery was <75%. However, the diagnostic accuracy predicted using the combined optimal cut-off values at 1 and 3 days after orthopedic surgery was ~94%, which was significantly higher than the accuracy calculated using single optimal cut-off values (P<0.05). These results suggest that the diagnostic accuracy predicted using combined optimal cut-off values is significantly higher than that predicted using single optimal cut-off values.

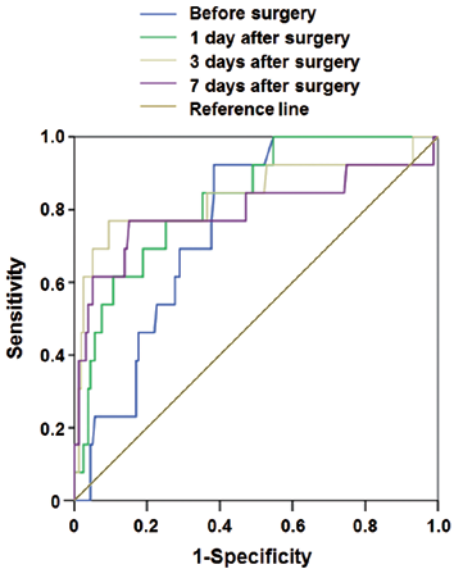


Figure 4. Receiver operating curve analysis of the prediction of deep vein thrombosis using plasma D-dimer expression levels 1 day prior, and 1, 3 and 7 days after orthopedic surgery.

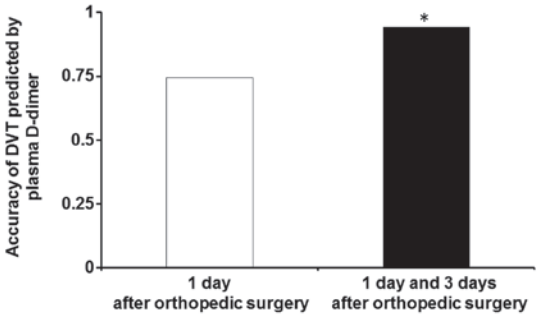


Figure 5. Diagnostic accuracy of the prediction of deep vein thrombosis (DVT) using optimal cut-off values of plasma D-dimer expression levels. Error bars represent standard error of the mean. *P<0.05 vs. 1 day.

## Discussion

DVT is a complication of orthopedic surgery that accounts for the onset of >50% of pulmonary embolisms (16). Each year, the mortality resulting from pulmonary embolisms caused by DVT is ~0.5% (17), and early prevention and accurate diagnosis is key to reducing the morbidity and mortality of DVT. Color Doppler ultrasonography is the preferred method used in the clinical diagnosis of DVT as it is a non-invasive and repeatable procedure (18). The diagnostic accuracy of color Doppler ultrasonography of DVT is 97% (19); however, it is a time-consuming and uncomfortable process for the patient, who is required to repeatedly move throughout the examination.

The measurement of plasma D-dimer expression levels is a simple and low-cost procedure. In addition, the procedure can be repeated and dynamically observed in the same patient. However, a method for determining the critical detection time and the optimal cut-off value of plasma D-dimer expression levels in orthopedic patients is urgently required.

In the present study, plasma D-dimer expression levels were recorded in DVT and non-DVT groups prior to and following orthopedic surgery. The results indicate that the detection of plasma D-dimer expression levels in orthopedic patients 1 day after surgery may be important in the prediction of DVT. ROC

analysis results of plasma D-dimer expression levels at different time points prior to and following orthopedic surgery demonstrated that the area under the ROC curve of plasma D-dimer expression levels 1 day after orthopedic surgery was 0.889; the optimal cut-off value was 6,360 $\mu$g/l, and the threshold of the optimal cut-off value had a sensitivity of 92.9% and a specificity of 85%.

In the present study, plasma D-dimer expression levels differed between different time points, patients and types of surgery. Therefore, predicting DVT using plasma D-dimer expression levels at a single point has limitations and inaccuracies. Diagnostic accuracy predicted using combined optimal cut-off values at 1 and 3 days after orthopedic surgery was ~94%, which was significantly higher than that predicted using single optimal cut-off values.

In conclusion, the results from the present study suggest that the detection of plasma D-dimer expression levels 1 day after orthopedic surgery is important in the prediction of DVT. In addition, the diagnostic accuracy of DVT is significantly increased by the combined analysis with optimal cut-off values at 1 and 3 days after orthopedic surgery.

## References


1. Lyle CA, Gibson E, Lovejoy AE and Goldenberg NA: Acute prognostic factors for post-thrombotic syndrome in children with limb DVT: a bi-institutional cohort study. Thromb Res 131: 37-41, 2013.
2. Dua A, Neiva S and Sutherland A: Does previous varicose vein surgery alter deep vein thrombosis risk after lower limb arthroplasty? Orthop Surg 4: 222-226, 2012.
3. Shah K, Thevendran G, Younger A and Pinney SJ: Deep-vein thrombosis prophylaxis in foot and ankle surgery: What is the current state of practice? Foot Ankle Spec 10: 101-106, 2015.
4. Jeeshan RR, Ahmad M and Graham MTS: Subclavian vein thrombosis following acute internal fixation of a clavicular fracture. Shoulder Elbow 5: 108-110, 2013.
5. Wakabayashi H, Hasegawa M, Niimi R, Naito Y, Nakagawa T and Sudo A: Clinical analysis of preoperative deep vein thrombosis risk factors in patients with total hip arthroplasty. Thromb Res 136: 855-855, 2015.
6. Ozgur ES, Karaca K, Ozye C and Nayci SA: Does anatomic location of deep venous thrombosis affect the clinical findings and course in the patient of pulmonary embolism. Eur Respir J 38 (Suppl 55): 2345, 2011.
7. Mant MJ, Eurich DT, Russell DB and Majumdar SR: Post-thrombotic syndrome after total hip arthroplasty is uncommon. Acta Orthop 79: 794-799, 2008.
8. Struijk-Mulder MC, Ettema HB, Verheyen CC and Büller HR: Comparing consensus guidelines on thromboprophylaxis in orthopedic surgery. J Thromb Haemost 8: 678-683, 2010.
9. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR and Colwell CW; American College of Chest Physicians: Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133 (6 Suppl): S381-S453, 2008.
10. Tenna AM, Kappadath S and Stansby G: Diagnostic tests and strategies in venous thromboembolism. Phlebology 27 (Suppl 2): 43-52, 2012.
11. Molugu C, Fisher G, Hirons B, Hughes D and Raftery S: P151 V-DimERS Study - Value of D-Dimers in estimating risk of significant pulmonary embolism and deep vein thrombosis. Thorax 68 (Suppl 3): A144, 2013.
12. Aaron W and Ann V: Is the D-dimer test a viable option for the detection of PE? J Nucl Med 55: 2708, 2014.
13. Wells P: Overview and comparison of D-dimer assay kits for DVT and PE. Clin Adv Hematol Oncol 2: 160, 2004.
14. Lees D, Griffiths P, Paxton C and Wahbi Z: Can D-dimer assay, together with clinical probability predict computed tomography pulmonary angiogram (CTPA) outcomes for pulmonary embolism (PE)? Eur Respir J 38 (Suppl 55): 582, 2011.
15. Shimoyama Y, Sawai T, Tatsumi S, Nakahira J and Minami T: Examination of risk factors for deep vein thrombosis following total hip arthroplasty. Masui 60: 897-902, 2011 (In Japanese).
16. Park Y, Choi H, Kim SH, Kang J, Kang WC, Shin MS and Moon J: Multisite paradoxical embolisms in a patient with patent foramen ovale and pulmonary thromboembolism. Int J Cardiol 159: e29-e31, 2012.
17. Wu O, Clark P, Lowe GD, Walker ID and Greer IA; Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study Group: Thrombophilia and venous thromboembolism after total hip or knee replacement surgery: A systematic review. J Thromb Haemost 3: 811-813, 2005.
18. Lausen I, Jensen R, Wille-Jørgensen P, Jørgensen L, Rasmussen M, Lyng K, Andersen M and Raaschou H: Colour Doppler flow imaging ultrasonography versus venography as screening method for asymptomatic postoperative deep venous thrombosis. Original. European Journal of Radiology 20: 200-204, 1995.
19. Magnusson MB, Nelzén O, Risberg B and Sivertsson R: A colour Doppler ultrasound study of venous reflux in patients with chronic leg ulcers. European Journal of Vascular and Endovascular Surgery 21: 353-360, 2001.