

 **Original Article** 

Clinical Course of Asymptomatic Isolated Distal Deep Vein Thrombosis of the Leg: A Single-Institution Study

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Background: The natural history of asymptomatic isolated distal deep vein thrombosis (DVT) of the leg is unclear. This study aimed to describe a 3-month and 1-year clinical course after diagnosis of asymptomatic isolated distal DVT of the leg.

Methods: This study included 127 patients with asymptomatic, sonographically proven isolated distal DVT who did not receive anticoagulant therapy and were retrospectively evaluated at our hospital between May 2014 and September 2016. After 3 months and 1 year, the presence or absence of venous thromboembolism recurrence and extension of DVT toward proximal veins was sonographically confirmed.

Results: At 3-month and 1-year follow-ups, 125 and 109 patients were observed, respectively. All patients showed no symptoms or findings suspecting venous thromboembolism recurrence during the observation period. However, 43 patients underwent repeat ultrasonic examination, and thrombus extension was confirmed in 2 patients.

Conclusions: Asymptomatic isolated distal DVT of the leg showed good prognosis, and thus uniform anticoagulation

therapy was considered unnecessary. (This is a translation of *Jpn J Phlebol* 2018; 29(3): 309–314.)

Keywords: deep vein thrombosis, isolated distal deep thrombosis, anticoagulant therapy, asymptomatic

Introduction

Deep vein thrombosis (DVT) cases can be classified into proximal DVT, in which the thrombus is found in a vein proximal to the popliteal vein, and distal DVT, in which the thrombus is localized in lower leg veins (tibial veins and peroneal veins) and intramuscular veins (soleal veins and gastrocnemius veins).¹⁾ In Japan, since ultrasounds can be performed relatively easily on the lower limbs due to advances in equipment and technology, many asymptomatic distal DVT cases are detected adventitiously, reportedly accounting for about half of DVT diagnoses.^{2,3)} While the natural history and treatment of symptomatic distal DVT have been described in many papers,^{4–6)} no reports have documented studies conducted specifically on patients with asymptomatic distal DVT, partly because screening for asymptomatic DVT is not recommended outside of Japan.^{7,8)} Asymptomatic distal DVT is expected to be less severe than symptomatic DVT, and anticoagulant therapy has been reported to be ineffective in a randomized controlled trial in low-risk patients with symptomatic distal DVT.⁹⁾ Here we report results of a retrospective study on the prognoses of patients with asymptomatic distal DVT who were followed up at our hospital without anticoagulant therapy.

Subjects and Methods

Of 2,015 limbs of 1,177 patients who underwent an ultrasound of the lower limbs for suspected DVT at our hospital between May 2014 and September 2016, those diagnosed with primary distal DVT were included in this study.

During the study period, 277 patients/336 limbs were

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diagnosed with primary DVT. Of these, we excluded 133 patients (147 limbs), diagnosed with proximal DVT, and 8 patients (16 limbs), diagnosed with bilateral DVT, in which a proximal thrombus was found in a lower limb, and a distal thrombus was found in the contralateral lower limb. We also excluded six patients (10 limbs) who were found to have distal DVT during lower limb ultrasound, after being diagnosed with symptomatic pulmonary embolism, and one patient (two limbs) who was sonographically proven to have distal DVT in the lower limbs after being diagnosed with asymptomatic pulmonary embolism. This was because the observed thrombus was highly likely to be the remaining thrombus in the lower leg after embolization of the proximal DVT. Two patients (two limbs) with symptomatic distal DVT who underwent anticoagulant therapy were also excluded. Ultimately, this retrospective study included 159 limbs of 127 patients with asymptomatic distal DVT (Fig. 1). The “asymptomatic” condition was defined as the absence of symptoms attributable to DVT. Specifically, “asymptomatic” DVT patients include those who have lower leg swelling and pain but in whom the localized thrombus is highly unlikely to be responsible for the swelling based on its location and size, the site of pain is unrelated to the position of thrombosis, or symptoms are attributable to other diseases. None of the asymptomatic distal DVT patients included in this study underwent anticoagulant therapy. In addition, aspirin was not administered to treat DVT. Patients with edema wore elastic stockings or elastic bandages to alleviate it.

Data collected from medical records and telephone interviews with patients or their family members included: patient’s age, sex, risk factors, reason for lower limb examination as well as survival, symptomatic venous thromboembolism (VTE) (affected or not), and thrombus extension on ultrasonography (detected or not) at three months and one year after diagnosis. The ultrasound equipment mainly used was LOGIQ E9 (GE Healthcare Japan, Tokyo, Japan), equipped with a 7.5 MHz–12 MHz probe, or Aplio 500 (Toshiba Medical Systems, Tochigi,

Japan). Compression, color Doppler, and pulse Doppler methods were mainly used for sonographic DVT screening to search for chronic thrombi in lower legs. Thrombus age was estimated based on the fact that an acute-phase thrombus is hypoechoic, widens the blood vessel, and is soft enough to change its shape upon compression by the probe, while a chronic-phase thrombus is hyperechoic, is shrunk to induce vasoconstriction, and is hard enough for its shape be unaltered upon compression.¹⁰⁾

Results

The study included 159 limbs of 127 patients with asymptomatic distal DVT; 35 patients were male and 92 patients were female. The participants’ mean age was 75.5 (± 11.5) years. As risk factors, 21.6% (21 patients) were obese, as defined based on a BMI of 25 or higher, 29.9% (38 patients) were cancer patients, and 15.7% (20 patients) long-term (≥4 days) bedridden patients; all patients other than these bedridden patients were ambulatory. Inpatients accounted for 47.2% (60 patients). Compression therapy with elastic stockings or elastic bandages was used for 71.7% (91 patients). Oral aspirin was used for 12.6% (16 patients) (Table 1).

The most common reason for performing ultrasound was lower limb edema, which accounted for 39% of the patients. The DVT screening test was performed because of a high D-dimer level and as part of preoperative testing in 26.7% (34 patients) and 22.0% (28 patients), respectively. The examination was performed for lower limb pain, but revealed thrombi in positions other than the pain sites in 11.8% (15 patients); these patients were considered to have incidental distal DVT (Fig. 2).

DVT was detected in the right lower limb in 47 cases, in the left lower limb in 48 cases, and in both lower limbs in 32 cases. The thrombus was located in the soleal vein in 138 limbs, the gastrocnemius vein in 13 limbs, the tibial vein in 8 limbs, and the peroneal vein in 30 limbs. Thrombi were found simultaneously in the soleal and peroneal veins in 13 lower limbs, soleal and gastrocnemius veins in six lower limbs, soleal and tibial veins in one lower

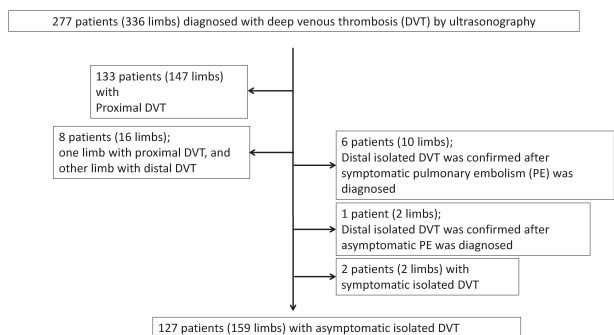


Fig. 1 Flow chart of patients’ assessment.

Table 1 Patient characteristics

Baseline characteristics	
Gender (male/female) (n=127)	35/92
Age (years average±SD) (n=127)	75.5±11.5
BMI (kg/m ² average±SD) (n=97)	22.8±4.8
BMI ≥ 25 kg/m ² (n=97) (%)	21.6 (n=21)
Cancer at diagnosis (%) (n=127)	29.9 (n=38)
Bed rest (%) (n=127)	15.7 (n=20)
Hospitalization at diagnosis (%) (n=127)	47.2 (n=60)
Usage of compression stockings or elastic bandage (%) (n=127)	71.7 (n=91)
Patients who take Aspirin (%) (n=127)	12.6 (n=16)

limb, gastrocnemius and peroneal veins in one lower limb, and peroneal and tibial veins, soleal, gastrocnemius, and peroneal veins in one lower limb, and soleal, peroneal, and tibial veins in one lower limb; more than 80% of thrombi were found in the soleal vein (Fig. 3). According to lower limb ultrasonography, thrombi were estimated to be chronic-phase for 123 limbs (77%) and acute-phase for 22 limbs (Fig. 4).

Three-month and 12-month follow-up data were available for 125 and 109 patients, respectively. Two patients died of a disease unrelated to VTE during the three-month observation period (one died of cancer), and 15 during the 12-month observation period (eight died of cancer); the outcome could not be confirmed for one patient. In all patients who were diagnosed as either acute or chronic, no symptoms or findings suggestive of VTE recurrence were

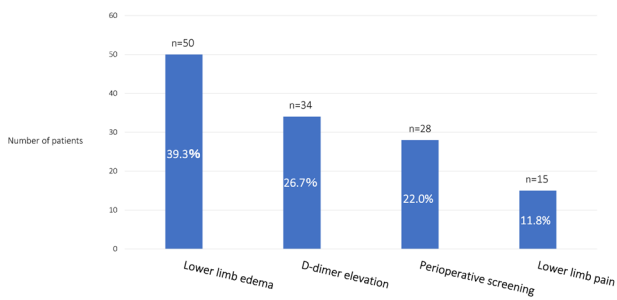


Fig. 2 Reasons for performing an ultrasonographic examination.

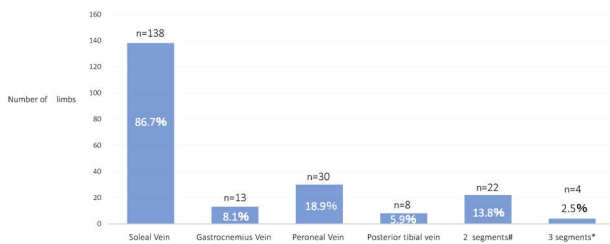


Fig. 3 Location of isolated distal deep vein thrombosis.
 #Soleal vein+gastrocnemius vein, soleal vein+peroneal vein, soleal vein+posterior tibial vein, gastrocnemius vein+peroneal vein and peroneal vein+posterior tibial vein.
 *Soleal vein+gastrocnemius vein+peroneal vein and soleal vein+peroneal vein+posterior tibial vein.

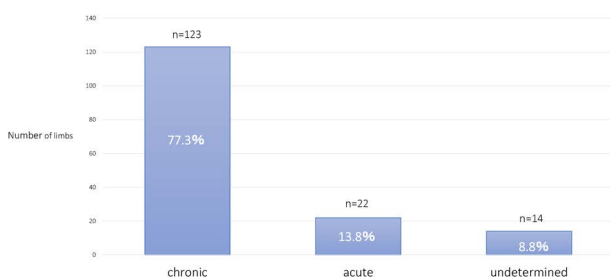


Fig. 4 Sonographic imaging of thrombosis.

observed, and no diagnoses of VTE were made during the observation period (Table 2). Follow-up lower limb vein ultrasounds were performed for 43 patients (56 limbs). Among these patients/limbs, proximal extension of the thrombus was observed in one limb with acute-phase thrombosis, a new thrombus was found at a different proximal site in one limb with chronic-phase thrombosis, and new distal DVT was found in one patient (one limb) with chronic-phase thrombosis (Table 3). Thrombi remained unchanged in characteristics and position in 39 limbs, regressed in seven limbs, and disappeared in seven limbs. Acute-phase thrombi tended to regress more commonly, while chronic-phase thrombi tended to remain unchanged. Proximal extension occurred in a 77-year-old female patient who temporarily became long-term bedridden, due to subarachnoid hemorrhage, and underwent a screening examination for both lower limbs. The initial ultrasound of the lower limbs revealed acute-phase thrombi in the gastrocnemius vein of the right lower limb and in the soleal and gastrocnemius veins of the left lower limb. The lower limb ultrasound, performed one year later, showed the regressed thrombus in the right lower limb and a chronic-phase, continuous, regressed mural thrombus in the popliteal and superficial femoral veins. The patient in the case where a new thrombus was found at a different proximal site was a 96-year-old woman. Ultrasonography performed for close examination of edema in the left lower limb revealed a chronic-phase thrombus in the soleal vein; one year later, an isolated, regressed chronic-phase thrombus was found in the left femoral vein. The patient in the case where a new distal DVT was found was

Table 2 Venous thromboembolism recurrence

	3-month (n=125*)	12-month (n=109#)
Numbers of venous thromboembolism recurrence	0	0

* 2 patients died because of another disease.

15 patients died because of another disease, and 1 patient was lost at follow-up.

Table 3 Results of thrombus propagation

Status of thrombus (n=56)	Chronic	Acute
No change	39	0
Retraction	0	7
Disappearance	6	1
New thrombus (proximal DVT)#	1	0
New thrombus (isolated distal DVT)*	1	0
Propagation to popliteal vein+	0	1

#New thrombosis was confirmed in a remote proximal vein.

*New thrombosis was confirmed in another isolated distal vein.

+ Thrombosis extended to the popliteal vein.

a 72-year-old woman with ovarian cancer, peritoneal dissemination. The initial examination ultrasound performed due to a high D-dimer level revealed a regressed chronic-phase thrombus in the soleal vein of the right lower limb and no thrombus in the left lower limb; the ultrasound performed six months later showed a chronic-phase thrombus in the soleal vein of the left lower limb.

Discussion

In this paper, we defined “asymptomatic” more narrowly as the absence of symptoms due to DVT. Specifically, “asymptomatic” DVT patients include those who have lower leg swelling and pain but in whom the localized thrombus is highly unlikely to be responsible for lower leg swelling based on its location and size, the site of pain being unrelated to the position of thrombosis, or symptoms being attributable to other diseases. In some previous papers,¹¹⁾ patients were examined because of lower limb pain, swelling, or tenderness were also included as “symptomatic DVT” cases. The definition of asymptomatic DVT used in this paper was broader than in other reports. Nevertheless, our definition appears to be more appropriate for determining the DVT treatment strategy.

Asymptomatic distal DVT reportedly has a good prognosis even without therapeutic doses of anticoagulants.^{12,13)} However, no consensus has been reached on a standard treatment strategy, and this issue has not been investigated adequately. The 8th edition of the American College of Chest Physician guidelines (ACCP) has recommended three-month anticoagulant therapy for distal DVT.¹⁴⁾ In the subsequently published 9th-edition of ACCP guidelines, perioperative DVT screening has not been recommended for asymptomatic patients in departments of orthopedic surgery or general surgery because the clinical benefits have not been demonstrated^{7,8)}; this edition of the guidelines recommended ultrasound testing follow-up for patients at low VTE risk and anticoagulant therapy for patients at high VTE risk, with an additional statement that anticoagulant therapy is not indicated for all cases of symptomatic distal DVT.¹⁵⁾ The NICE guidelines in the UK did not cover distal DVT because it does not develop into a severe condition.¹⁶⁾ This is based on the finding that the distal DVT prognosis is more favorable than that previously reported.^{4,5)}

In Japan, ultrasounds of veins in lower limbs are often performed for medical safety reasons, with questionnaire surveys showing that distal DVT accounted for about 50% of all cases, many of which were asymptomatic.^{2,3)} Yamashita et al. have studied asymptomatic DVT patients and reported that 70% were the distal type.¹¹⁾ Since proximal-type cases are commonly symptomatic, and distal-type cases are often asymptomatic, it reasonable to

consider that many distal DVT cases are asymptomatic.¹⁷⁾ In Japan, DVT is frequently found through screening examinations, with 60%–65.3% of cases reportedly found during orthopedic surgery on the lower limbs,^{18,19)} and 20.8% during major abdominal surgery.²⁰⁾ Distal veins below the popliteal vein are mainly affected. Therefore, the actual incidence of asymptomatic distal DVT may be high in high-risk patients such as those in the perioperative period. Meanwhile, uniform DVT screening and perioperative anticoagulant therapy are performed only for high-risk patients hospitalized in some institutions because of limited insurance coverage and bleeding risk. Nevertheless, the incidence of perioperative symptomatic pulmonary embolism is 3.1 in 10,000, according to a report from the Japanese Society of Anesthesiologists, which is lower than the rate of discovery of asymptomatic DVT in screening.²¹⁾ Therefore, among patients with asymptomatic distal DVT, the incidence of symptomatic VTE is predicted to be low even if anticoagulant therapy is not performed.

The thrombus age can be estimated with a certain accuracy based on the echoic intensity and level of regression of the thrombus.¹⁰⁾ The DVT recurrence rate has been known to decrease in the chronic phase,²²⁾ while it is high early after the onset, and the benefit initiating anticoagulant therapy for chronic-phase DVT has not been demonstrated. In the present study, 78% of thrombi found in asymptomatic cases of lower leg DVT were chronic.

Recent reports have shown that uniform anticoagulant therapy or prolonged treatment for symptomatic or asymptomatic distal DVT was ineffective for preventing clinical VTE and proximal thrombus extension and only increased bleeding complications.^{9,16)}

In this study, asymptomatic distal DVT was considered low-risk, and all patients were followed up without anticoagulant therapy; no symptomatic VTE occurred during the follow-up period. Therefore, anticoagulant therapy for asymptomatic distal DVT is not appreciably beneficial or more likely to be harmful, at least for low-risk patients. In this study, 29% of the sample (38 patients) overall were cancer patients, and no relapses and proximal extension were observed. Therefore, high-risk patients were included, but accounted for a small portion. A previous study has shown that anticoagulant therapy for asymptomatic DVT significantly decreased occurrence and recurrence of symptomatic VTE in cancer patients, although the study included proximal cases also.¹⁶⁾ There may be room for anticoagulant therapy after considering the balance between likely therapeutic benefits and risk for hemorrhagic complications for some asymptomatic distal DVT patients at high VTE risk.

Lower limb ultrasound detected thrombus extension in one patient, recurrence in the proximal side in one

patient, and recurrence in the distal side in one patient. Studies conducted outside of Japan have found extension to proximal veins in 3%–3.7% over the natural course in cases of distal thrombosis, including symptomatic cases.^{4,5)} According to a phlebology survey conducted in Japan, thrombus extension to the proximal side was found in 27 (3.6%) of 759 distal DVT patients, including some symptomatic patients who underwent anticoagulant therapy.²⁾ In the present study in patients with asymptomatic lower leg DVT who did not undergo anticoagulant therapy, proximal extension occurred in one patient (1.7%), or in two patients (3.6%) including a case in which a new thrombus was found in the proximal side. Thus, the incidence of proximal extension was lower than, or comparable to, that of previous surveys. However, the cases in which thrombus extension was found were asymptomatic, and those were chronic-phase thrombi that regressed without anticoagulant therapy. Therefore, when asymptomatic distal DVT patients are discovered, follow-up examinations for possible clinical VTE and sonographic proximal extension appear to be appropriate, since proximal extension can occur among these patients, albeit rarely.

The present study was a single-center retrospective case review that included a variety of patients, such as those with few risk factors. Going forward, a larger scale case review of asymptomatic distal DVT with high VTE risk is desirable.

Conclusions

A good prognosis was noted for patients with asymptomatic distal DVT who were followed up without anticoagulant therapy.

Disclosure Statement

The authors do not have any conflicts of interest to disclose with regards to this article.

References

- 1) Ando M, Ito M, Ohgi S, et al. Guidelines for the diagnosis, treatment and prevention of pulmonary thromboembolism and deep vein thrombosis (JCS 2009 revised edition) (in Japanese)
- 2) Yamada N, Yamaki T, Iwata H, et al. Current status of treatment of deep vein thrombosis localized in the lower leg in Japan (Japanese Society of Phlebology survey research report). *Jpn J Phlebol* 2013; **24**: 211. (in Japanese)
- 3) Satokawa H, Yamaki T, Iwata H, et al. The survey of deep vein thrombosis and venous thromboembolism prevention: Japanese vein study XIII. *Jpn J Phlebol* 2012; **23**: 271-81. (in Japanese)
- 4) MacDonald PS, Kahn SR, Miller N, et al. Short-term natural history of isolated gastrocnemius and soleal vein thrombosis. *J Vasc Surg* 2003; **37**: 523-7.
- 5) Schwarz T, Buschmann L, Beyer J, et al. Therapy of isolated calf muscle vein thrombosis a randomized, controlled study. *J Vasc Surg* 2010; **52**: 1246-50.
- 6) Horner D, Hogg K, Body R, et al. The anticoagulation of calf thrombosis (ACT) project. *Chest* 2014; **146**: 1468-77.
- 7) Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; **141 Suppl**: e278S-325S.
- 8) Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; **141 Suppl**: e227S-77S.
- 9) Righini M, Galanaud JP, Guennequy H, et al. Anticoagulant therapy for symptomatic calf deep vein thrombosis (CACTUS): a randomised, double-blind, placebo-controlled trial. *Lancet Haematol* 2016; **3**: e556-62.
- 10) Meissner MH, Moneta G, Burnand K, et al. The hemodynamics and diagnosis of venous disease. *J Vasc Surg* 2007; **46 Suppl S**: 4S-24S.
- 11) Yamashita Y, Shiomi H, Morimoto T, et al. Asymptomatic lower extremity deep vein thrombosis. *Circ J* 2017; **81**: 1936-44.
- 12) Kearon C. Natural history of venous thromboembolism. *Circulation* 2003; **107 Suppl 1**: I22-30.
- 13) Singh K, Yakoub D, Giangola P, et al. Early follow-up and treatment recommendations for isolated calf deep venous thrombosis. *J Vasc Surg* 2012; **55**: 136-40.
- 14) Kearon C, Kahn SR, Agnelli G, et al. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians evidence-based clinical practice guidelines (8th ed). *Chest* 2008; **133 Suppl**: 454S-545S.
- 15) Kearon C, Akl EA, Comerota AJ, 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**: e419S-96S.
- 16) Gerard S, Roshan A, Susan B, et al.; National Clinical Guideline Centre (UK). Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing. London: Royal College of Physicians (UK), 2012.
- 17) Rose SC, Zwiebel WJ, Miller FJ. Distribution of acute lower extremity deep venous thrombosis in symptomatic and asymptomatic patients. *J Ultrasound Med* 1994; **13**: 243-50.
- 18) Fuji T, Ochi T, Niwa S, et al. Prevention of postoperative venous thromboembolism in Japanese patients undergoing total hip or knee arthroplasty: two randomized, double-blind, placebo-controlled studies with three dosage regimens of enoxaparin. *J Orthop Sci* 2008; **13**: 442-51.
- 19) Fuji T, Fujita S. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism after hip fracture surgery. *Journal of Japanese Society for Fracture Repair* 2008; **30**: 206-9. (in Japanese)
- 20) Sakon M, Maehara Y, Yoshikawa H, et al. Incidence of ve-

- nous thromboembolism following major abdominal surgery: a multi-center, prospective epidemiological study in Japan. *J Thromb Haemost* 2006; 4: 581-6.
- 21) Kuroiwa M, Morimatsu H, Tsuzaki K, et al. Changes in the incidence, case fatality rate, and characteristics of symptomatic perioperative pulmonary thromboembolism in Japan: results of the 2002–2011 Japanese Society of Anesthesiologists perioperative pulmonary thromboembolism (JSA-PTE) study. *J Anesth* 2015; 29: 433-41.
- 22) Breddin HK, Hach-Wunderle V, Nakov R, et al. Effects of a low-molecular-weight heparin on thrombus regression and recurrent thromboembolism in patients with deep-vein thrombosis. *N Engl J Med* 2001; 344: 626-31.