Clinical presentation of isolated calf deep vein thrombosis in inpatients and prevalence of associated pulmonary embolism

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ABSTRACT

Objective: Controversy exists regarding the clinical significance and optimal treatment of isolated calf deep vein thrombosis (DVT). In the present study, the clinical presentation of isolated calf DVT and the association of isolated calf DVT with pulmonary embolism (PE) in hospitalized patients were investigated.

Methods: A total of 1435 hospitalized patients had undergone whole leg duplex ultrasound between January 2018 and June 2020. Isolated calf vein DVT was diagnosed in 135 of these 1435 patients.

Results: The soleal vein was the most frequently involved (52.6%). Thrombus was detected only in the axial veins in 57 patients (42.2%), muscular veins in 46 patients (34.4%), and both axial and muscular veins in 32 patients (23.7%). Of the 135 patients, 44 (32.6%) had undergone recent orthopedic surgery, 31 (23.0%) had active cancer, and 22 (16.3%) had a history of recent stroke. The reasons for duplex ultrasound examination were leg edema and/or pain for 57 patients (42.2%), the diagnosis of PE for 33 (24.4%), and an elevated D-dimer level for 27 patients (20.0%). For 16 patients (11.9%), DVT had been diagnosed as an incidental finding on imaging studies performed for other purposes. Of the 135 patients, 96 (71.1%) had received anticoagulation therapy. Concurrent PE was diagnosed in 45 patients (33.3%), 14 of whom had had lesions in the main pulmonary artery. Of the 45 patients with concurrent PE, 35 had not experienced leg edema and/or pain. Recurrent venous thromboembolism was observed in four patients (3.0%) at a mean follow-up of 15.5 ± 12.7 months.

Conclusions: In the present study, isolated calf DVT was associated with a high prevalence of PE in the hospitalized patients. Patients with isolated calf DVT, even without leg edema and/or pain, could have concurrent PE. Anticoagulation therapy should be considered for inpatients with isolated calf DVT. The muscular veins were frequently involved and, thus, should be thoroughly evaluated with imaging studies. (J Vasc Surg Venous Lymphat Disord 2022;■:1-7.)

Keywords: Inpatient; Lower extremity; Venous thrombosis

The optimal treatment of isolated calf deep vein thrombosis (DVT) has remained unclear. The American College of Chest Physicians (ACCP) guidelines for antithrombotic therapy for venous thromboembolism (VTE) have suggested two different treatment options.[1] Anticoagulation therapy has been recommended for symptomatic patients with a risk factor for proximal extension. Serial duplex ultrasound within 2 weeks has been recommended for patients without severe symptoms or risk factors for extension.[1] However, the level of evidence for these recommendations is low. In addition, decisions regarding the treatment modality can be inconsistent because of the alternate options available for care. Thus, significant variation has resulted in the management of isolated calf DVT.[2]

Conflicting results have been reported on the efficacy of anticoagulation therapy to reduce venous thromboembolic events in patients with isolated calf DVT. Utter et al[3] analyzed 384 patients with isolated calf DVT and showed a reduced incidence of proximal DVT and pulmonary embolism (PE) when isolated calf DVT was treated with anticoagulant agents.[3] Yoon et al[4] also showed that therapeutic anticoagulation significantly reduced the incidence of VTE complications compared with surveillance or prophylactic anticoagulation therapy.[4] However, a recent randomized controlled trial (RCT) showed that low-molecular-weight heparin was not superior to placebo in reducing the risk of proximal extension or thromboembolic events for patients with symptomatic calf DVT.[5]

A recent study found the muscular calf veins were the most frequently involved veins in hospital-acquired DVT and might be the origin of the DVT.[6] Sartori et al[7] also showed that isolated calf DVT was more prevalent than proximal DVT in hospitalized patients. Although it has been widely accepted that, overall, isolated calf DVT will be benign and self-limiting, the clinical significance of isolated calf DVT could be different for hospitalized patients.[8] In the present study, the clinical presentation and treatment patterns of isolated calf DVT for real-world

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inpatients were investigated to identify the prevalence of concurrent PE in hospitalized patients with isolated calf DVT.

METHODS

Study population and duplex ultrasound. Patients with a diagnosis of isolated calf DVT using duplex ultrasound between January 2018 and June 2020 were included in the present study, which was performed at the Chung-Ang University Hospital, a tertiary referral hospital in South Korea. Three surgeons involved in patient care determined the need for duplex ultrasound from the physical examination findings and clinical presentation of each patient. The duplex ultrasound scans were performed by two vascular surgeons. Whole leg duplex ultrasound was performed from the distal external iliac vein to the calf veins and included the axial veins (ie, tibioperoneal trunk, posterior tibial vein, anterior tibial vein, peroneal vein) and muscular veins (ie, soleal veins, gastrocnemius veins). Isolated calf DVT was defined as acute thrombosis in one or more deep veins distal to the popliteal vein. Proximal DVT was defined as acute thrombosis located in the popliteal vein, femoral vein, iliac vein, and/or inferior vena cava. The presence of an incompressible venous segment, echogenic material in the lumen, or the absence of color flow was defined as acute thrombosis. The patients who had received anticoagulant therapy before duplex ultrasound for other causes, such as PE or atrial fibrillation, and those with a diagnosis of chronic DVT were excluded from the present study. The Chung-Ang University Hospital institutional review board approved the present study (approval no. 2105-005-19366). The review board also waived the requirement for patient informed consent because the research would pose no more than a minimal risk to the patients and would result in no adverse patient effects.

Clinical data collection. A retrospective analysis of the patients' medical records was performed. Data on the baseline demographics, risk factors for DVT (eg, active cancer, recent trauma or surgery), and comorbidities were collected. The reason for duplex ultrasound was reviewed and classified into four categories: leg edema and/or pain, elevated D-dimer level, a diagnosis of PE, and incidental findings on imaging studies performed for other purposes. The involved veins, laterality, and prevalence of concurrent PE were reviewed. The laboratory test results, including the hemoglobin and D-dimer levels, were collected. The initial treatment modalities were reviewed and classified into four categories: anticoagulation therapy, serial duplex ultrasound, observation, and inferior vena cava (IVC) filter placement. The results from any follow-up duplex ultrasound scans were evaluated. The recurrence of VTE and all-cause mortality during follow-up were also reviewed.

ARTICLE HIGHLIGHTS

- **Type of Research:** A single-center, retrospective study
- **Key Findings:** In 135 hospitalized patients with a diagnosis of isolated calf deep vein thrombosis (DVT), the soleal vein was the most frequently involved (52.6%). Concurrent pulmonary embolism had been diagnosed in 45 patients, 14 of whom had had lesions in the main pulmonary artery.
- **Take Home Message:** Isolated calf DVT was associated with a high prevalence of pulmonary embolism in hospitalized patients; thus, anticoagulation therapy should be considered for inpatients with isolated calf DVT. The calf muscular vein branches should be thoroughly evaluated because soleal vein DVT was the most frequent form of isolated calf vein DVT.

Statistical analysis. Continuous data are summarized as the mean ± standard deviation and were compared using the t test. Categorical data are summarized as the frequencies and proportions and were compared using the χ^2 test. Statistical significance was set at $P < .05$. Logistic regression analysis was performed to investigate the variables associated with concurrent PE or recurrent VTE. Variables from the univariate analyses with $P < .20$ were considered for inclusion in the final multivariable model. All statistical analyses were performed using SPSS software, version 26.0 (IBM Corp, Armonk, NY).

RESULTS

Clinical presentation. A total of 1435 patients had undergone duplex ultrasound during the study period, with 634 examined during their hospitalization. Of these 634 patients, 135 were diagnosed with isolated calf vein DVT and 136 with proximal or both proximal and calf DVTs. The prevalence of DVT and isolated calf DVT among the hospitalized patients who had undergone duplex ultrasound was 42.8% (271 of 634 patients) and 21.3% (135 of 634 patients), respectively. Of the 135 patients with isolated calf DVT, 44 (32.6%) had undergone recent orthopedic surgery, 31 (23.0%) were receiving treatment for active cancer, and 22 (16.3%) had a history of recent stroke (Table I).

For the 634 hospitalized patients, duplex ultrasound had been performed because of leg edema and/or pain in 463 (73.0%), elevated D-dimer levels in 62 (9.8 %), and PEs observed using computed tomography (CT) in 61 (9.6%). In addition, 48 patients (7.6%) had undergone duplex ultrasound for surveillance of a previously diagnosed DVT. In the 135 hospitalized patients with isolated calf DVT, duplex ultrasound was performed because of leg edema and/or pain in 57 patients (42.2%) and elevated D-dimer levels in 27 patients (20.0%). Isolated calf DVT was found as an incidental result on

Table I. Baseline characteristics (n = 135)

Variable	Mean ± SD or No. (%)
Age, years	74.4 ± 11.9
Female sex	99 (73.3)
BMI, kg/m^2	24.3 ± 4.2
Recent trauma	25 (18.5)
Recent surgery	56 (41.5)
Orthopedic	44 (32.6)
Abdominal	7 (5.2)
Other	5 (3.7)
Active cancer	31 (23.0)
Hepatobiliary	8 (5.9)
Gastrointestinal	6 (4.4)
Lung	6 (4.4)
Hematologic	5 (3.7)
Gynecologic or genitourinary	4 (3.0)
Other	2 (1.4)
Hypertension	78 (57.8)
Diabetes mellitus	35 (25.9)
Coronary artery disease	13 (9.6)
Stroke	22 (16.3)
History of VTE	5 (3.7)

BMI, Body mass index; *SD*, standard deviation; *VTE*, venous thromboembolism.

Table II. Clinical presentation and anatomic location of isolated calf deep vein thrombosis (DVT; n = 135)

Variable	No. (%) or Mean ± SD
Reason for duplex ultrasound	
Leg edema and/or pain	57 (42.2)
Elevated D-dimer level	27 (20.0)
After PE diagnosis	33 (24.4)
Incidental finding from imaging study performed for other purposes	16 (11.9)
Unknown	2 (1.5)
D-dimer level, μg/mL	4.1 ± 2.3
Involved vein	
Axial	57 (42.2)
Muscular	46 (34.1)
Both	32 (23.7)
Laterality	
Right	50 (37.0)
Left	43 (31.9)
Both	42 (31.1)
Concurrent PE	
Main	14 (10.4)
Segmental	23 (17.0)
Subsegmental	8 (5.9)
Not found	90 (66.7)

PE, Pulmonary embolism; *SD*, standard deviation.

duplex ultrasound for indications other than a DVT evaluation, such as varicose veins or orthopedic disease in 16 patients (11.9%). Finally, 33 patients (24.4%) had been referred for duplex ultrasound because PEs had been found on CT scans performed for respiratory symptoms or cancer (Table II).

The mean D-dimer level for 113 patients was 4.1 ± 2.3 μg/mL (fibrinogen-equivalent units; normal range, 0-0.5 μg/mL). Only four patients had had D-dimer levels within the normal range. Of these four patients, one had undergone duplex ultrasound to evaluate for leg edema and one after a diagnosis of PE. For the remaining two patients, the isolated calf DVT was an incidental finding.

Anatomic distribution of the involved veins. In the patients with isolated calf DVT, the most involved vein was the soleal veins (n = 71; 52.6%). When the patients were grouped according to the involvement of the axial and/or muscular veins, the axial veins were more frequently involved. Thrombus was detected in only the axial veins in 57 patients (42.2%), only the muscular veins in 46 patients (34.4%), and both the axial and the muscular veins in 32 patients (23.7%). Unilateral right-sided thrombi (37.0%) were more frequent than unilateral left-sided thrombi (31.9%) or bilateral thrombi (31.1%). Patients with leg edema and/or pain had a greater prevalence of thrombus in the muscular veins than had the patients without leg edema and/or pain (52.6% vs 21.1%; $P = .001$; Table III).

Concurrent PE. Of the 271 patients with a diagnosis of DVT, including both proximal and calf DVTs, concurrent PE was diagnosed in 85 patients (31.4%). Of the 135 patients with isolated calf DVT, concurrent PE was diagnosed in 45 patients (33.3%). All the patients were diagnosed with PE using CT, and none had undergone ventilation/perfusion scans or pulmonary arteriography. Of these 45 patients, 14 had had lesions in the main pulmonary artery. Of the 45 patients with isolated calf DVT and concurrent PE, 33 had been referred for duplex ultrasound because of PE observed on CT scans. In 12 patients, subsequent PE had been found a few days after the DVT diagnosis, 11 of whom had received anticoagulation therapy. One patient had been treated with IVC filter insertion owing to the high risk of bleeding. Finally, of the 45 patients with concurrent PE, 35 had not experienced leg edema and/or pain before the diagnosis.

Treatment modality. Of the 135 patients, 96 (71.1%) had received anticoagulation therapy, including direct oral anticoagulant agents for 85 patients (88.5%). The mean duration of anticoagulation therapy was 5.8 ± 7.2 months (median, 3 month; range, 1-33 months). Bleeding complications from anticoagulation therapy occurred in eight patients. None of the patients developed major bleeding.

Table III. Subgroup analysis of anatomic distribution

Variable	Involved vein			*P* value
	Axial vein	Muscular vein	Both	
Leg edema and/or pain				.001
Yes (n = 57)	17 (29.8)	30 (52.6)	10 (17.5)	
No (n = 76)	39 (51.3)	16 (21.1)	21 (27.6)	
Unknown (n = 2)	1 (50)	0 (0)	1 (50)	
Cancer				.278
Active cancer (n = 26)	9 (34.6)	8 (30.8)	9 (34.6)	
History of cancer (n = 5)	4 (80.0)	1 (20.2)	0 (0)	
No history of cancer (n = 104)	44 (42.3)	37 (35.6)	23 (22.1)	
Recent surgery				.843
Yes (n = 56)	25 (44.6)	19 (33.9)	12 (21.4)	
No (n = 79)	32 (40.5)	27 (34.2)	20 (25.3)	

Data presented as number (%).

Of the 135 patients, 10 (7.4%) had been initially followed up with serial duplex ultrasound examinations without anticoagulation therapy. Three had subsequently received anticoagulation therapy after serial duplex ultrasound examinations showed progression of calf DVT. Another 10 patients (7.4%) had undergone IVC filter placement, and 7 had received anticoagulation therapy after the risk of bleeding had decreased. In addition, 19 patients (14.0%) were observed without any intervention or serial duplex ultrasound examinations, and 6 patients were lost to follow-up. Of the 45 patients with concurrent PE, 41 had received anticoagulation therapy. Five patients had undergone IVC filter placement because of a high risk of bleeding, three of whom had received anticoagulation therapy after the bleeding risk had decreased.

Follow-up. The mean follow-up duration was 15.5 ± 12.7 months (median, 14 months; range, 1-41 months), and recurrent VTE was observed in four patients (3.0%). All four patients with recurrent VTE were women, and three had initially been treated with direct oral anticoagulant agents. Recurrent VTE was observed 3 to 11 months after the cessation of the anticoagulation therapy. Two patients were diagnosed with DVT during an ultrasound examination for orthopedic disease. These patients had undergone surgery after 3 months of anticoagulation therapy. However, recurrent VTE was observed after the orthopedic surgery. The details of the patients with recurrent VTE are summarized in Table IV.

All-cause mortality at 3 months and 1 year after the initial diagnosis of isolated calf DVT was 20.4% and 26.7%, respectively. None of the patients had died of VTE-related causes. Cancer progression was the most common cause of death.

Variables associated with concurrent PE and recurrent VTE. Logistic regression analysis was performed to investigate the variables associated with concurrent PE. On univariate analysis, multiple vein involvement and right-sided thrombi were associated with concurrent PE, and the body mass index, axial vein involvement, and D-dimer level >4.0 μg/mL (fibrinogen-equivalent units) showed tendency to be associated with concurrent PE. However, their significance was not retained on multivariate analysis (Table V). The four patients with recurrent VTE were women, and the right posterior tibial vein was involved in three of the four. However, the statistical power of the regression analysis for predicting the factors for recurrent VTE was low owing to the small number of recurrent cases.

DISCUSSION

Controversy exists regarding the clinical significance and optimal treatment of isolated calf DVT. Little is known about the natural history of isolated calf DVT. The findings from the present study have shown the clinical presentation of isolated calf DVT, especially for hospitalized patients. More than one half of the hospitalized patients with isolated calf DVT had not experienced leg edema and/or pain. One third of the patients with isolated calf DVT had had concurrent PE. In addition, 10% of the patients with PE had had lesions in the main pulmonary artery.

In the present study, the prevalence of concurrent PE was greater than that previously reported. The reported prevalence of PE concurrent with isolated calf DVT has ranged from 0% to 6.2%.[6] However, the included studies were heterogeneous in the imaging protocol used and diagnosis time points after isolated calf DVT. The present study included only hospitalized patients. In hospitalized patients, isolated calf vein DVT can be associated with higher rates of PE; thus, the performance of chest CT and anticoagulation therapy should be considered.[9] In addition, the present results showed that patients with isolated calf DVT, even without leg edema and/or pain,

Table IV. Patients with recurrent venous thromboembolism (VTE)

			Primary lesion					Recurrence	
Pt. No.	Age, years	Sex	Involved vein	Laterality	Concurrent PE	Risk factor for VTE	Initial treatment	Interval after AC cessation, months	Recurrent lesion
1	78	F	PTV, soleal, GN	Both	None	Cancer	AC therapy	3	Right popliteal vein
2	50	F	Soleal	Right	Main	None	AC therapy	10	PE
3	68	F	PTV	Right	None	Orthopedic surgery	Serial duplex ultrasound	11	Left common femoral vein, popliteal vein
4	68	F	PTV	Right	Segmental	Orthopedic surgery	AC therapy	3	Right PTV, peroneal vein, PE

AC, Anticoagulation; *F,* female; *GN,* gastrocnemius; *PE,* pulmonary embolism; *Pt. No.,* patient number; *PTV,* posterior tibial vein.

can have concurrent PE. Evaluation for DVT is necessary for hospitalized patients with elevated D-dimer levels, even if without leg edema and/or pain. In addition, reports of leg edema and/or pain can be delayed for physically inactive and hospitalized patients on bed rest. This could have caused a delay in anticoagulation therapy and the diagnosis of concurrent PE.

The likelihood of proximal propagation is important in determining the need for anticoagulation therapy for isolated calf DVT. Some have suggested that DVT will begin in the calf veins and that isolated calf DVT in patients with PE is a remnant of a more proximally embolized thrombus.[9-11] Studies of the natural history of isolated calf DVT have indicated that one fourth to one third of symptomatic calf DVTs will propagate into the proximal venous system.[10] In the present study, 10 patients had initially undergone serial duplex ultrasound studies without anticoagulation therapy. The ultrasound studies showed proximal propagation in 3 of these 10 patients, who had finally received anticoagulation therapy. The absolute risk of clot propagation and embolization should be further investigated in future studies.

In the real world, most patients with isolated calf DVT will receive anticoagulation therapy. Fleck et al[9] showed that 90% of patients had received anticoagulation therapy after the initial diagnosis of isolated calf DVT. The present study had only included hospitalized patients, some of who had had active cancer. Inpatient status and active cancer are risk factors for proximal propagation.[12] These clinical situations can lead physicians to prescribe anticoagulation therapy rather than perform serial duplex ultrasound examinations. However, little is known regarding the appropriate duration of anticoagulation therapy. In an open-label RCT, 6- and 12-week anticoagulation therapy durations were compared, with no significant differences found in the recurrence rates.[13] Owing to the rarity of RCTs, the ACCP recommendation for antithrombotic therapy for VTE was determined from the results from a single study.[14]

A few RCTs have assessed the need for anticoagulation therapy for isolated calf DVT. An open-label RCT of 93 patients with isolated calf DVT showed that therapeutic anticoagulation resulted in an 11.4% relative risk reduction of VTE complications.[15] A recent RCT, the CACTUS (calf thrombosis diagnosed by ultrasound) trial, showed no benefit from anticoagulation therapy for symptomatic calf vein DVT.[5] However, the trial had excluded hospitalized patients and patients with active cancer.[5] Many of our hospitalized patients with isolated calf DVT had had a history of recent stroke or active cancer. The all-cause mortality rate for our study population was relatively high. The need for anticoagulation therapy should be considered for high-risk patients. According to the ACCP recommendations for antithrombotic therapy for symptomatic calf vein thrombosis, patients with active cancer and inpatients are at risk of calf DVT extension, warranting anticoagulation therapy.[1,16]

Few studies have reported on the recurrence of isolated calf DVT. A study using the OPTIMEV (optimisation de l'Interrogatoire dans l'evaluation durisque thromboembolique veineux) registry showed that the 3-year overall VTE recurrence rate was 2.7% in those with isolated calf DVT.[17] Also, age >50 years, unprovoked DVT, and multiple venous involvement were risk factors for recurrence.[17] In another single-center study of 90 patients, male sex and cancer were associated with high VTE recurrence in patients with distal calf DVT.[18] In the latter study, the recurrence rate of isolated calf vein DVT was 3.0%. In the present study, all the patients with recurrence were women, and the posterior tibial vein was involved most often. However, it has been challenging to investigate the risk factors for recurrence because of the small number of events. Further studies with larger numbers of patients are required to select patients with a higher risk of recurrence and the need for anticoagulation therapy.

The soleal vein was the most affected in the present study. Labropoulos et al[19] showed that thrombi confined to muscular veins were common. The soleal

Table V. Factors associated with concurrent pulmonary embolism (PE)

	Univariate			Multivariate		
Factor	OR	95% CI	*P* value	OR	95% CI	*P* value
Age >75 years	0.544	0.263-1.127	.101	0.856	0.349-2.100	.734
Female sex	1.375	0.622-3.042	.431	NA	NA	NS
BMI >25 kg/m^2	1.958	0.894-4.291	.093	2.205	0.861-5.649	.100
Recent surgery	0.815	0.391-1.699	.585	NA	NA	NS
Active cancer	1.304	0.537-3.165	.558	NA	NA	NS
Recent stroke	2.026	0788-5.211	.143	2.306	0.719-7.398	.160
History of VTE	1.333	0.215-8.281	.758	NA	NA	NS
Involved vein, axial vein	2.003	0.898-4.467	.089	1.258	0.442-3.580	.667
Multiple veins	2.240	1.062-4.724	.034	1.792	0.625-5.136	.277
Laterality, right	2.357	1.010-5.502	.047	1.207	0.407-3.584	.734
D-dimer >4 μg/mL (FEU)	2.278	0.986-5.260	.054	1.699	0.676-4.269	.260

BMI, Body mass index; *CI,* confidence interval; *FEU,* fibrinogen-equivalent units; *NA,* not applicable; *NS,* not significant; *OR,* odds ratio.

vein connects to the posterior tibial and peroneal veins; thus, the thrombus can propagate to an axial vein. Kret et al[11] showed that 25% of isolated calf muscular vein thrombosis had propagated or was associated with a new thrombus in a remote site. In a study of 128 patients with calf muscular DVT, 18.8% of the patients had experienced VTE recurrence, with a mean follow-up of 27 months.[20] No differences were found in the prevalence of concurrent PE between the patients with axial vs muscular vein calf DVT; thus, both axial and muscular vein calf DVT should be considered to be potentially associated with PE and treated equally. In addition, the present study has shown that thrombi in muscular veins will cause leg edema and/or pain more frequently than will thrombi confined to axial veins.

The present study had several limitations. First, owing to the retrospective nature of the present study, selection bias could have been present. Second, the total number of VTE recurrences was small, which lowered the statistical power to identify the risk factors for recurrence. Third, some patients had been diagnosed with isolated calf DVT after PE; thus, it is possible that a proximal thrombus had embolized and that only the distal components remained. Finally, no interobserver variability was assessed for the duplex ultrasound findings.

CONCLUSIONS

Isolated calf DVT is not rare, and the prevalence of concurrent PE was high in the hospitalized patients in the present study. The absence of leg edema and/or pain does not preclude the presence of concurrent PE for hospitalized patients with isolated calf DVT. Anticoagulation therapy should be considered for those with isolated calf DVT, especially for hospitalized patients. The muscular veins were frequently involved and had a similar association with concurrent PE; thus, muscular calf veins should undergo imaging studies and be equally considered for treatment compared with axial veins. The risk factors for VTE recurrence and the optimal duration of anticoagulation therapy for isolated calf DVT requires investigation in future studies.

AUTHOR CONTRIBUTIONS

Conception and design: SK
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Critical revision of the article: SK
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