Article

Not peer-reviewed version

Association of Post-Thrombotic Changes with Disease Severity in Patients Presenting with Symptomatic Calf Vein Thrombosis

Spiro Odysseas Koustas * and Nicos Labropoulos *

Posted Date: 28 July 2025

doi: 10.20944/preprints202507.2306.v1

Keywords: calf vein thrombosis; duplex scanning; recanalization; reflux development; post-thrombotic signs and symptoms

 doi:10.20944/preprints202507.2306.v1

Article

Association of Post-Thrombotic Changes with Disease Severity in Patients Presenting with Symptomatic Calf Vein Thrombosis

Spiro Koustas [1] and Nicos Labropoulos [1]

[1] Division of Vascular and Endovascular Surgery, Department of Surgery, Stony Brook University Hospital, Stony Brook, NY, USA

* Correspondence: spiro.koustas@stonybrookmedicine.edu (S.O.K.); nlabrop@yahoo.com (N.L.)

Abstract

Background/Objectives: This prospective study was designed to evaluate the natural history of isolated calf deep vein thrombosis (ICDVT) in relation to their patterns and distribution. **Methods:** 117 limbs in 104 patients, with isolated symptomatic calf vein thrombosis were included in the study. These were objectively diagnosed with ultrasound. The distribution and extent of the initial DVT was recorded in detail. Patients with a documented episode of prior DVT or those having thrombus in the popliteal vein or higher were excluded. Follow-up at 3-48 months was performed with clinical examination and ultrasound. Ultrasound examination was done with the patient in the standing position to ensure optimal testing for detecting post-thrombotic changes. Affected venous segments were classified as having an occlusion, complete recanalization, partial recanalization, with or without reflux. **Results:** At 1 year, out of 98 limbs analyzed, most (99%) had recanalization of their calf vein thrombosis; 53% (n=52) had complete, 46% (n=45) had partial, and 1% (n=1) had no recanalization. Ultrasound studies of those limbs showed reflux (R) in 22% (n=22), obstruction (O) in 9% (n=9), R + O in 33% (n=32), and normal findings in 36% (n=35) of limbs. Only 17% of limbs had signs of edema (CEAP 3), 2% had skin changes (CEAP 4) and 0% had any signs of ulcers (CEAP 5,6). Of these findings, only 14 patients experienced persistent symptoms at 1 year. **Conclusions:** Patients with symptomatic calf vein DVT generally have good clinical outcomes, with most being asymptomatic, and having mild disease. While small deterioration is seen up to 4 years, few limbs developed skin changes. The presence of reflux in calf veins does not appear to be a significant predictor of severe disease development in the medium term.

Keywords: calf vein thrombosis; duplex scanning; recanalization; reflux development; post-thrombotic signs and symptoms

1. Introduction

Isolated calf deep vein thrombosis (ICDVT) is often seen in clinical practice. It accounts for at least one third of all lower limb DVT [1,2]. Complications of ICDVT include pulmonary embolism (PE), thrombus propagation to proximal veins, recurrent DVT, and post-thrombotic syndrome (PTS). The latter can lead to chronic patient suffering that may reduce their quality of life [3,4]. PTS after ICDVT includes most of the signs and symptoms seen in patients with chronic venous disease (CVD). While several studies have examined the clinical course of isolated distal DVT, their conclusions vary with reported outcomes ranging from benign and self-limited to severe. Notably, no studies to date have objectively correlated duplex ultrasound findings of post-thrombotic damage with the development of associated clinical signs and symptoms.

This prospective study was designed to evaluate the natural history of symptomatic isolated calf DVT in relation to their patterns and distribution. It further analyzes the prospective correlation of progression in clinical class with changes in duplex ultrasound (DU) and clinical symptoms.

 doi:10.20944/preprints202507.2306.v1

2. Materials and Methods

2.1. Patient Selection

In this prospective study, patients with a documented episode of an isolated symptomatic calf vein DVT were selected. This was the first lower extremity episode for these patients, which was objectively diagnosed by duplex ultrasound imaging. Clinical symptoms at presentation included swelling, dull or localized pain, heaviness, pulling, throbbing and warmth of the lower extremity. Patients with a documented episode of prior DVT of the symptomatic limb, or those having thrombus in the popliteal vein or higher, as well as those who propagated to popliteal vein after enrolment were excluded. Additionally, those with fixed joint abnormalities or limited range of motion, immobility (wheelchair-bound or the use of assisted devices to walk), chronic inflammation (skin disorders, vasculitis), lymphangitis, lymphedema, lipedema, superficial vein thrombosis and those with previous vein procedures of the lower limb including stripping, ligation, ablation, phlebectomy, thrombectomy, or thrombolysis were also excluded.

2.2. Ultrasonography Investigation

DU examination of both legs was performed by experienced certified vascular technologists each having done >1000 DVT exams prior to the study. All veins from the external iliac to the calf were evaluated in the supine position with slight head elevation. Patients with suboptimal calf vein imaging in the supine position were examined while seated to improve the visualization of the veins. The transverse plane was used to scan the entire length of the posterior tibial, anterior tibial, gastrocnemius and soleal veins. The diagnosis of DVT was based on the presence of intraluminal material, inability to compress the vein, luminal dilation and filling defects on color mode.

At the chronic stage the patients were evaluated for reflux and obstruction. The ultrasound examination was performed in the standing and sitting positions. In these positions, there is a higher hydrostatic column, where the veins have a larger diameter and their evaluation is more physiologic. The threshold for defining reflux of the calf veins was >0.5 seconds [5]. Reflux was induced by manual compression distal to the imaging site followed by sudden release. The compression was applied at least 10 cm away to avoid interference at the area of evaluation. If the compression was not adequate, the patient was asked to perform a forceful dorsi/plantar flexion. Doppler tracings were obtained always in the longitudinal view and with a proper angle of insonation to get the best possible signal. The scale was optimized to the height of the Doppler trace while the Doppler gain was set having a dark background.

The distribution and extent of obstruction at the calf veins was done in the seating position. The affected venous segments were classified as having an occlusion, partial recanalization, and complete recanalization. Occlusion was defined based on lack of vein compressibility, filling defects on color mode, and visible luminal material with no detectable flow within the affected vein segment. Partial recanalization was characterized when the vein was partially compressible, with visible luminal material and the identification of at least one flow channel within the thrombus with spontaneous flow or flow observed after distal augmentation. Complete recanalization was determined when the vein appeared widely patent, had full compressibility and no filling defects on color doppler.

2.3. Documentation of Post-Thrombotic Changes with Disease Severity

Clinic visits were scheduled at 3, 6, 12 months and yearly thereafter for 4 years. Patients had a comprehensive clinical examination as well as DU imaging during their clinic visits. Additional clinical evaluations and DUS were performed as needed when new signs and symptoms of VTE emerged. The causes of thrombosis were recorded in detail. These included common risk factors of VTE such as trauma, surgery, malignancy, thrombophilia, and prolonged travel. The CEAP classification system was utilized to clinically grade the severity of disease [6]. Skin changes defined as $CEAP_{1-3}$ were categorized as mild to moderate PTS, while $CEAP_{4-6}$ was classified as severe PTS.

 doi:10.20944/preprints202507.2306.v1

2.4. Statistical Anaylsis

Descriptive statistics were used for the patients' characteristics. Differences in proportions were compared with a chi square test and the Fisher exact test when the value in any of the cells was <5. Both tests were two-tailed and the level of significance was set at $p<0.05$. In this study no sample size calculations were made and no interim analysis was performed.

3. Results

There were 117 limbs in 104 symptomatic patients (49 men and 55 women) who had a mean age of 54 years (range 21-86). The reasons for the isolated calf DVT are listed in **Table 1**. Most patients (n=45) had trauma or surgery and 32 had an unprovoked DVT. The most common location of DVT was the peroneal vein (n=49), but not significantly different from the PTV (n=34) and Soleal (n=39). Thrombus in the gastrocnemial vein was found in 27 limbs. Thrombus in ATV was found in only 2 limbs and on both occasions, it was in combination with other vein segments. About 1/3 of limbs had thrombi in more than one vein. Anticoagulation and elastic compression stockings was prescribed in 61 patients, whereas 35 were prescribed elastic compression stockings and antiplatelets. There were 8 patients that were prescribed only elastic compression stockings. This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn.

Table 1. Causes of thrombosis.

Cause	Patients
Unprovoked	**32**
Trauma	**11**
Surgery	**34**
Cancer	**12**
Pregnancy	**4**
Travel >4 hours	**8***
Unknown	**3**
Total	**104**

*3 of them were on oral contraceptives. .

Partial or complete recanalization was found in all but 3 patients at 3-6 months (**Table 2)**. Reflux, obstruction, or the combination of the two was found in about 2/3 of patients, while 1/3 was normal (**Table 3**). Most patients had mild disease. Only 2 patients had skin changes (both C4a) and none developed an ulcer. Of the 17 limbs that developed edema, in 15 it was mild and located in the malleoli and only in 2 was moderate extending to the lower calf. Presence of symptoms was found only in 14 patients at 1 year. Feeling of heaviness towards the end of the day was the most common symptom. No patient developed severe pain or claudication.

Table 2. Extent of recanalization over 4 years.

Recanalization	3-6 Months	12 Months	24 Months	36 Months	48 Months
Complete	**49**	**52**	**29**	**17**	**10**
Partial	**55**	**45**	**37**	**21**	**12**
None	**3**	**1**	**1**	**0**	**0**
Total	**107**	**98**	**67**	**38**	**22**

 doi:10.20944/preprints202507.2306.v1

Table 3. Duplex Ultrasound changes over 4 years .

	3-6 Months	12 Months	24 Months	36 Months	48 Months
Reflux (R)	**21**	**22**	**18**	**8**	**4**
Obstruction (O)	**19**	**9**	**3**	**2**	**1**
R + O	**29**	**32**	**25**	**17**	**9**
Normal	**38**	**35**	**21**	**11**	**8**
Total	**107**	**98**	**67**	**38**	**22**

Correlation of progression in clinical class with changes in DU were studied up to 4 years. The CEAP class and symptoms over 4 years are displayed in **Table 4**.

Patients with reflux or a combination of reflux and obstruction were more likely to develop symptoms as seen in **Table 5**. Prevalence of symptoms somewhat increased over time, but it was far from being significant.

Table 4. Severity of disease using the CEAP classification system along with the prevalence of symptoms at over 4 years .

Class	12 Months	24 Months	36 Months	48 Months
0,1	**7**	**8**	**4**	**2**
2	**1**	**1**	**1**	**2**
3	**5**	**6**	**4**	**2**
4	**1**	**1**	**1**	**1**
5	**0**	**0**	**0**	**0**
6	**0**	**0**	**0**	**0**
Total	**14**	**16**	**10**	**7**

Table 5. Reflux and obstruction with associated prevalence of symptoms .

	12 months	Symptoms	24 months	Symptoms	36 months	Symptoms	48 months	Symptoms
Reflux	**22**	**5**	**18**	**4**	**8**	**2**	**4**	**1**
Obstruction	**9**	**1**	**3**	**0**	**2**	**0**	**1**	**0**
R+O	**32**	**7**	**25**	**7**	**17**	**6**	**9**	**4**
Normal	**35**	**1**	**21**	**0**	**11**	**0**	**8**	**0**
Total	**98**	**14**	**67**	**11**	**38**	**8**	**22**	**5**

4. Discussion

The natural history of ICDVT has been extensively studied. Duplex ultrasound changes over time have also been reported. However, prospective correlation of progression in clinical class and symptoms with changes in DU has not been reported. This study includes a well characterized patient cohort with a first episode of documented ICDVT where the PTS signs and symptoms in relation to changes observed by US were analyzed.

The cohort was selected based on a reasonable life expectancy to ensure sufficient time for documentation of the progression and severity of PTS. Those with chronic immobility were excluded from the study as this is an independent risk factor for developing chronic venous disease. Additionally, patients with a history of thrombosis or those with thrombus in the popliteal vein or higher were excluded as it has been shown that patients that experience ipsilateral recurrent DVT have an increased risk of developing PTS as well as experience greater severity of symptoms [7]. This reduces unaccounted factors that may have led to progression in severity of disease in our cohort.

 doi:10.20944/preprints202507.2306.v1

The current study found that almost all limbs had partial or complete recanalization at 1 year. Recanalization rates in the calf veins are expected to be high and have been reported by others [3,8]. Typically, this rate is higher when compared to proximal veins. Yamaki et al., showed that recanalization in the calf veins was faster when compared to femoropopliteal veins [9]. The recanalization pattern observed in our study was likely due to the direct effect of the calf muscle pump and the lesser thrombus load compared to the proximal veins [11,12]. It has been shown that calf muscle pump generates higher pressure over the veins compared to the thigh muscle pump [11]. Van Ramshorst et al demonstrated that both thrombus resolution and recanalization appeared to be a function of the initial thrombus load [12].

In our study only 2 limbs had mild skin damage and none developed an ulcer. Most limbs had mild to moderate disease and only 14 patients experienced persistent symptoms at 1 year with barely any changes seen in the following years. This may be due to the faster recanalization rates in the distal veins and the lesser thrombus load compared to proximal DVT [10]. Progression in CEAP classification, presence and severity symptoms may be due to the extent of thrombotic involvement, particularly when multiple calf veins are affected. These findings were observed in Labropoulos et al., which demonstrated thrombosis in multiple calf veins resulted in a greater severity of PTS compared to thrombosis in a single calf vein [7]. The better clinical outcome in this study is also that many factors that could contribute to a worse outcome such as reduced mobility, previous DVT, edema, venous interventions in the affected limb were excluded.

Reflux and/or obstruction were found in 63 limbs and the rest 35 were normal. Johnson et al. concluded that the coexistence of residual reflux and residual partial or complete obstruction in the major deep veins was more likely to be associated with the development of PTS [13]. Further studies have shown that only reflux in the deep veins were more likely associated with the development of PTS [14,15,16]. This was seen in our study where patients with reflux or a combination of reflux and obstruction were more likely to develop symptoms. Moreover, Yamaki et al 2009., showed that the calf venous blood filling index as well as the venous ejection index and venous retention index (as strong predictors of PTS) were significantly increased in patients with iliofemoral DVT as compared to those with calf DVT [17]. Similarly, this was observed in our study with isolated calf vein DVT, where only 2 limbs had mild skin damage and none developed an ulcer at one year.

This study has some limitations. Factors that influence the development of CVD such as lack of physical activity, obesity, age, and musculoskeletal problems were not considered. Although a good sample size was available at the 1-year follow-up, not all patients followed up to the 4 year completion DUS and clinical examination. This subsequently led to a small sample size at 4 years and thus was not included within the analysis. Over time, the proportion of symptomatic patients appeared to increase, likely reflecting a lower follow-up rate among asymptomatic individuals and thus a relative rise in symptomatic case representation. Asymptomatic patients with similar DVT distribution and extent were not included to determine if their natural history was comparable. We did not perform plethysmography to assess the overall impact of reflux and/or obstruction nor the efficiency of the calf muscle pump in the affected extremity. Although we included the signs and symptoms of the DVT, we did not perform quality of life measurements. Patients receiving parenteral anticoagulation were not subject to a controlled protocol as it was at the discretion of the treating physician. Similarly, the use of antiplatelet therapy was not a controlled variable as administration varied according to individual clinical indications. All patients were strongly encouraged to use 20-30 mm Hg knee high compression stockings at the time of diagnosis and subsequent visits, but we did not monitor their use. A hypercoagulable workup was performed selectively and was not available for all patients.

5. Conclusions

Patients with symptomatic calf vein DVT generally have good clinical outcomes, with most being asymptomatic and having mild disease. While small deterioration is seen up to 4 years, few

 doi:10.20944/preprints202507.2306.v1

limbs developed skin changes. The presence of reflux in calf veins does not appear to be a significant predictor of severe disease development in the medium term.

Author Contributions: Conceptualization NL; methodology, NL; formal analysis, NL, SK; investigation, NL.; writing—original draft preparation, SK, NL.; writing—review and editing, SK, NL.; project administration, NL; All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by Stony Brook Medicine Institutional Review Board. IRB number: IRB2023-00143.

Data Availability Statement: The data supporting the findings of this study were obtained from the local institutional electronic medical records (EMR) system. These data are not publicly available due to patient privacy and ethical restrictions.

Acknowledgments: The authors have reviewed and edited the output and take full responsibility for the content of this publication.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ICDVT	Isolated calf deep vein thrombosis
DVT	Deep Vein Thrombosis
PTS	Post-thrombotic syndrome
CEAP	Clinical Etiologic Anatomic Pathophysiologic
PE	Pulmonary Embolism
CVD	Chronic venous disease
DU	Duplex ultrasound
ATV	Anterior tibial vein
VTE	Venous thromboembolism
PTV	Posterior tibial vein

References

1. Labropoulos N, Webb KM, Kang SS, et al. Patterns and distribution of isolated calf deep vein thrombosis. *J Vasc Surg*. 1999;30(5):787-791. doi:10.1016/s0741-5214(99)70002-9.
2. Righini M. Is it worth diagnosing and treating distal deep vein thrombosis? No. *J Thromb Haemost*. 2007;5 Suppl 1:55-59. doi:10.1111/j.1538-7836.2007.02468.x
3. Garry J, Duke A, Labropoulos N. Systematic review of the complications following isolated calf deep vein thrombosis. Br J Surg. 2016 Jun;103(7):789-96. doi: 10.1002/bjs.10152. Epub 2016 Apr 6. PMID: 27060255.
4. Masuda EM, Kistner RL, Musikasinthorn C, Liquido F, Geling O, He Q. The controversy of managing calf vein thrombosis. J Vasc Surg. 2012 Feb;55(2):550-61. doi: 10.1016/j.jvs.2011.05.092. Epub 2011 Oct 26. PMID: 22032881.
5. Labropoulos N, Tiongson J, Pryor L, Tassiopoulos AK, Kang SS, Ashraf Mansour M, Baker WH. Definition of venous reflux in lower-extremity veins. J Vasc Surg. 2003 Oct;38(4):793-8. doi: 10.1016/s0741-5214(03)00424-5. PMID: 14560232.
6. Lurie F, Passman M, Meisner M, Dalsing M, Masuda E, Welch H, Bush RL, Blebea J, Carpentier PH, De Maeseneer M, Gasparis A, Labropoulos N, Marston WA, Rafetto J, Santiago F, Shortell C, Uhl JF, Urbanek T, van Rij A, Eklof B, Gloviczki P, Kistner R, Lawrence P, Moneta G, Padberg F, Perrin M, Wakefield T. The 2020 update of the CEAP classification system and reporting standards. J Vasc Surg Venous Lymphat Disord. 2020 May;8(3):342-352. doi: 10.1016/j.jvsv.2019.12.075. Epub 2020 Feb 27. Erratum in: J Vasc Surg Venous Lymphat Disord. 2021 Jan;9(1):288. doi: 10.1016/j.jvsv.2020.11.002. PMID: 32113854.

 doi:10.20944/preprints202507.2306.v1

7. Labropoulos N, Waggoner T, Sammis W, Samali S, Pappas PJ. The effect of venous thrombus location and extent on the development of post-thrombotic signs and symptoms. J Vasc Surg. 2008 Aug;48(2):407-12. doi: 10.1016/j.jvs.2008.03.016. Epub 2008 Jun 2. PMID: 18515036.
8. Sartori M, Lessiani G, Favaretto E, Migliaccio L, Iotti M, Giusto L, Ghirarduzzi A, Palareti G, Cosmi B. Ultrasound Characteristics of Calf Deep Vein Thrombosis and Residual Vein Obstruction After Low Molecular Weight Heparin Treatment. Eur J Vasc Endovasc Surg. 2016 Nov;52(5):658-664. doi: 10.1016/j.ejvs.2016.07.022. Epub 2016 Sep 7. PMID: 27614551.
9. Yamaki T, Nozaki M. Patterns of venous insufficiency after an acute deep vein thrombosis. J Am Coll Surg. 2005 Aug;201(2):231-8. doi: 10.1016/j.jamcollsurg.2004.12.014. PMID: 16038821.
10. Asbeutah AM, Riha AZ, Cameron JD, McGrath BP. Five-year outcome study of deep vein thrombosis in the lower limbs. J Vasc Surg. 2004 Dec;40(6):1184-9. doi: 10.1016/j.jvs.2004.10.025. PMID: 15622373.
11. Williams KJ, Ayekoloye O, Moore HM, Davies AH. The calf muscle pump revisited. J Vasc Surg Venous Lymphat Disord. 2014 Jul;2(3):329-34.
12. Van Ramshorst B, van Bemmelen PS, Hoeneveld H, Faber JA, Eikelboom BC. Thrombus regression in deep venous thrombosis. Quantification of spontaneous thrombolysis with duplex scanning. Circulation. 1992 Aug;86(2):414-9. doi: 10.1161/01.cir.86.2.414. PMID: 1638710.
13. Johnson BF, Manzo RA, Bergelin RO, Strandness DE Jr. Relationship between changes in the deep venous system and the development of the postthrombotic syndrome after an acute episode of lower limb deep vein thrombosis: a one- to six-year follow-up. *J Vasc Surg*. 1995;21(2):307-313. doi:10.1016/s0741-5214(95)70271-7
14. Killewich LA, Martin R, Cramer M, Beach KW, Strandness DE Jr. An objective assessment of the physiologic changes in the postthrombotic syndrome. *Arch Surg*. 1985;120(4):424-426. doi:10.1001/archsurg.1985.01390280018003
15. Haenen JH, Janssen MC, van Langen H, et al. The postthrombotic syndrome in relation to venous hemodynamics, as measured by means of duplex scanning and strain-gauge plethysmography. *J Vasc Surg*. 1999;29(6):1071-1076. doi:10.1016/s0741-5214(99)70248-x
16. Labropoulos N, Patel PJ, Tiongson JE, Pryor L, Leon LR Jr, Tassiopoulos AK. Patterns of venous reflux and obstruction in patients with skin damage due to chronic venous disease. Vasc Endovascular Surg. 2007;41(1):33-40. doi:10.1177/1538574406296246
17. Yamaki T, Nozaki M, Sakurai H, et al. Prognostic impact of calf muscle near-infrared spectroscopy in patients with a first episode of deep vein thrombosis. *J Thromb Haemost*. 2009;7(9):1506-1513. doi:10.1111/j.1538-7836.2009.03528.x