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Clinical Features and Associated Outcomes of Isolated Calf Vein Thrombosis From a Five-Year Tertiary Medical Center Experience: An Analytical Retrospective Cohort Study

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Abstract

BACKGROUND: The significance of isolated calf deep vein thrombosis (ICDVT) remains unclear with current guidelines not being based on strong level of evidence. Given the uncertainties, the therapeutic approaches vary among institutions; hence, it is prudent to look at existing experience of an institution where examination of calf veins is routinely done during venous duplex ultrasound of the lower extremities.

METHODS: Using an analytical retrospective cohort design, this study investigated the clinical profile and outcomes of patients noted to have ICDVT on venous duplex scan at a single tertiary center from October 1, 2018 to June 30, 2023.

RESULTS: A total of 151 subjects were included in the study. Most of the cases had either stabilization (36.42%, 95% CI: 28.75%-44.64%) or complete resolution (35.76%, 95% CI: 28.14%-43.96%) of ICDVT. Recurrence occurred in 15.89% (95% CI: 10.46%-22.72%) while proximal DVT extension only occurred in 10.60% (95% CI: 6.18-16.64%) of the subjects. None of the factors studied, including therapeutic management, were significantly associated with proximal DVT extension, recurrence, pulmonary embolism and stabilization of ICDVT. When it comes to resolution of ICDVT, only therapeutic management was found to have significant association.

CONCLUSION: Previously cited medical risk factors do not play a role in the development of ICDVT complications. While anticoagulation contributes to resolution of ICDVT, it can safely be managed conservatively in cases of high bleeding risk.

KEYWORDS: Calf vein thrombosis, anticoagulation

INTRODUCTION

Isolated calf deep vein thrombosis (ICDVT), defined as a thrombus confined to the infra-popliteal veins of the lower extremities without extension to proximal veins,[1] is a common occurrence in several studies, approaching half, if not more, of all cases of deep vein thrombosis (DVT) diagnosed by venous duplex scan.[2-4] Despite the number of individuals diagnosed with ICDVT, it is not as extensively studied as proximal DVT. Whether its clinical significance is similar to the latter, remains a matter of discussion. In the American College of Chest Physician's 9th edition of the Antithrombotic Therapy and Prevention of Thrombosis (AT9), routine examination of distal veins in patients with low-risk features is not encouraged because it is said that thrombosis in these segments, if present, is unlikely to cause complications.[5]

Several studies have looked into the risk factors and natural course of ICDVT in terms of extension and embolic potential, but the results were mostly inconclusive. Many of these studies were conducted among hospitalized patients who may have already had pre-existing conditions that predisposed them to develop DVT. In contrast, this study enrolled both in- and out-patients; thus, expanding the scope of what is already known about the matter. The importance of establishing risk factors and natural course of ICDVT lies in the fact that

anticoagulation, the primary treatment strategy, carries bleeding risks which must be weighed against its potential benefits.

Unfortunately, the current guidelines on management of ICDVT are not based on a strong level of evidence. Most of the large-scale studies have been conducted among the non-Asian population. Among Asian patients, the incidence of venous thromboembolism was reported to be lower, bringing into question whether to follow the same treatment strategies that were employed in previous studies.[6] Given these uncertainties, the therapeutic approaches vary among institutions; hence, it is noteworthy to look at the existing experience of an institution where examination of calf veins is routinely done during venous duplex ultrasound of the lower extremities. The early outcomes of these patients, as well as how they were managed in this particular setting, can be a reference for future clinical decision-making when it comes to appropriate management, pending availability of guidelines with strong level of evidence. Furthermore, to our knowledge, the present study covered the longest period (five years) conducted at a single center, potentially providing more robust data that reduced potential biases that may have affected previous shorter-term studies.

METHODS

This was an observational retrospective cohort study that included all in- and out- patients with acute and subacute ICDVT in a single center in the last five years, from October 1, 2018 to June 30, 2023. The study abided by the Principles of the Declaration of Helsinki (2013) and was granted approval by our institutional review board (Institutional Review Ethics Committee, St. Luke's Medical Center).

Potential subjects were selected retrospectively from the census of patients in the vascular laboratory who had significant findings on imaging studies. These findings were verified in the hospital's picture archiving and communications system (PACS) where images and official reports of venous duplex scans were stored. All venous duplex scan studies in our institution were performed by experienced sonographers. Our institution's protocol on venous duplex scan of the lower extremities required insonation of the distal external iliac artery down to the anterior and posterior tibial veins, usually in supine position. The calf veins were part of routine evaluation. Interpretation of studies was done by board-certified cardiologists with subspecialty in Vascular Medicine.

The demographic data, clinical profile, interventions and outcomes of each selected subject were retrieved from their electronic records. The following were excluded in the study: (1) Those with findings of a proximal DVT on previous venous duplex scan done in the past three months[4], (2) those with concomitant acute pulmonary embolism during the time of venous duplex scan on the assumption that findings may not represent a true isolated calf vein thrombosis but rather a probable remnant of more proximal thrombosis,[4] (3) those with concomitant acute superficial vein thrombosis measuring more than 5 cm in length and within 3 cm from the saphenofemoral junction since this may have high embolic potential warranting anticoagulation,[7] and (4) those with no available medical charts from where the clinical profile and outcomes can be derived.

The outcomes measured in this study, which were obtained from subsequent official ultrasound reports and medical charts, included proximal DVT extension, recurrence, pulmonary embolism, stabilization and resolution. The time to event that was used was anytime within 180 days as in several previous retrospective studies done on this subject.[2,8-9]

The PASS 2021 software was used to calculate minimum sample size. A minimum of 120 patients are required to achieve 90% statistical power using multiple logistic regression analysis with at most five factors, specifying a medium Cohen's effect size (f^2=0.15) and alpha set at 0.05. Stata MP version 17 software was used for data processing and analysis. Continuous variables were presented as median (interquartile range/IQR) due to non-normal distribution according to the Shapiro-Wilk test. Categorical variables were expressed as frequencies and percentages. To address sparse data bias, Firth's logistic regression analysis was conducted to determine factors associated with proximal DVT extension, recurrence and pulmonary embolism. Binary logistic regression was performed to determine factors associated with stabilization and resolution of ICDVT. Variables with $p<0.20$ in the simple logistic regression analysis were entered into the multiple logistic regression model. Model building was performed using backward elimination technique. P values ≤ 0.05 were considered statistically significant.

RESULTS

Patient Demographics

A total of 151 patients were included in the study. The baseline characteristics of patients are summarized in Table 1. Subjects were aged from 27 to 97 years old with a median of 70 years old. About half (51%) of the subjects were male. In terms of comorbidity, hypertension was present in 72% of subjects. Only six patients (2%) were either pregnant or had an abnormal hypercoagulability panel. Among the factors associated with clinical outcomes of ICDVT, inpatient status was the most prevalent, accounting for 87% of subjects, followed by active cancer in 38% of the cases.

Clinical and Anatomic Characteristics of ICDVT

As shown in Table 2, the most common reason for doing venous duplex scan was screening (53%). The soleal vein was involved in majority of the subjects (38%). Although 27% had more than one type of calf vein involvement, the soleal vein was still involved in most of the limbs. ICDVT occurred mostly in the right limb.

Clinical Outcomes and Associated Factors

Clinical outcomes were observed within 180 days from the diagnosis of ICDVT. Most of the cases had either stabilization

Table 1. Baseline Demographic Characteristics (n=151)

	n (%)
Age (in years), median	70 [IQR: 60-79]
Sex	
Female	74 (49)
Male	77 (51)
Comorbidities, %yes	
Hypertension	109 (72)
Diabetes mellitus	41 (27)
Coronary artery disease	18 (12)
Stroke	26 (17)
Hypercoagulable state, %yes	6 (4)
Risk Factors Associated with Clinical Outcomes of ICDVT, %yes	
Recent surgery	20 (13)
Presence of leg varicosities	10 (6)
Active cancer	58 (38)
History of DVT	18 (12)
Inpatient status	132 (87)

Table 2. Clinical Presentation and Anatomic Location of Isolated Calf Deep Vein Thrombosis (n=151)

Variable	n (%)
Reason for Duplex Scan	
Leg edema	39 (26)
Elevated D-dimer	15 (10)
Leg pain	17 (11)
Screening	80 (53)
Involved Vein	
Soleal	58 (38)
Gastrocnemius	27 (18)
Peroneal	16 (11)
Anterior tibial	0
Posterior tibial	9 (6)
More than one type of calf vein involvement	41 (27)
Soleal	29
Peroneal	26
Gastrocnemius	21
Anterior tibial	0
Posterior tibial	20
Laterality	
Right	61 (40)
Left	54 (36)
Both	36 (24)

(36.42%, 95% CI: 28.75%-44.64%) or complete resolution (35.76%, 95% CI: 28.14%-43.96%) of ICDVT. Recurrence was noted in 24 (15.89%, 95% CI: 10.46%-22.72%) patients and proximal DVT extension in 16 patients (10.6%, 10.60%, 95% CI: 6.18%-16.64%). It is noteworthy that only two patients developed pulmonary embolism having an incidence of 1.32% (95% CI: 0.16-4.70%). The average follow-up time was around 74 days from the time of diagnosis of ICDVT.

Several factors, including recent surgery, presence of leg varicosities, inpatient status, active cancer and therapeutic management, were analyzed for their association with clinical outcomes. Only 148 patients with complete data across all tested factors were included. None of the factors were significantly associated with proximal DVT extension (Table 3), recurrence (Table 4), pulmonary embolism (Table 5) and

Table 3. Factors Associated with Proximal DVT Extension (n=148)

	Proximal DVT extension		Logistic regression analysis[a]			
	Yes (n=16) n (%)	No (n=132) n (%)	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Recent surgery, yes *(Ref: No)*	1 (6)	19 (14)	0.56 (0.10-3.22)	0.519	-	-
Presence of leg varicosities, yes *(Ref: No)*	0	9 (7)	0.39 (0.02-7.09)	0.528	-	-
Inpatient status, yes *(Ref: No)*	15 (94)	117 (89)	1.36 (0.24-7.90)	0.730	-	-
Active cancer, yes *(Ref: No)*	8 (50)	50 (38)	1.63 (0.59-4.50)	0.342	-	-
Therapeutic management, Anticoagulation *(Ref: Conservative Management)*	11 (69)	82 (62)	1.28 (0.44-3.75)	0.653	-	-

Ref – reference category; [a]Firth's bias-corrected logistic regression was performed due to sparse data bias

Table 4. Factors Associated with Recurrence of ICDVT (n=148)

	Recurrence		Logistic regression analysis[a]			
	Yes (n=24) n (%)	**No (n=124) n (%)**	**Crude OR (95% CI)**	***P* value**	**Adjusted OR (95% CI)**	***P* value**
Recent surgery, *yes* *(Ref: No)*	4 (17)	16 (13)	1.44 (0.46-4.53)	0.530	-	-
Presence of leg varicosities, *yes* *(Ref: No)*	3 (13)	6 (5)	2.97 (0.75-11.78)	0.122	-	-
Inpatient status, *yes* *(Ref: No)*	24 (100)	108 (87)	7.45 (0.43-128.49)	0.167	-	-
Active cancer, yes *(Ref: No)*	8 (33)	50 (40)	0.76 (0.31-1.87)	0.551	-	-
Therapeutic Management, Anticoagulation (Ref: Conservative Management)	11 (46)	82 (66)	0.44- (0.18-1.05)	0.063	-	-

Ref – reference category; Firth's bias-corrected logistic regression was performed due to sparse data bias

Table 5. Factors Associated with Development of Pulmonary Embolism (n=148)

	Pulmonary embolism		Logistic regression analysis[a]			
	Yes (n=2) n (%)	**No (n=146) n (%)**	**Crude OR (95% CI)**	***P* value**	**Adjusted OR (95% CI)**	***P* value**
Recent surgery, yes *(Ref: No)*	1 (50)	19 (13)	6.54 (0.65-66.06)	0.112	-	-
Presence of leg varicosities, yes *(Ref: No)*	0	9 (6)	2.89 (0.13-64.69)	0.503	-	-
Inpatient status, yes *(Ref: No)*	2 (100)	130 (89)	0.63 (0.03-13.74)	0.770	-	-
Active cancer, yes *(Ref: No)*	0	58 (40)	0.30 (0.01-6.42)	0.443	-	-
Therapeutic Management, Anticoagulation *(Ref: Conservative Management)*	1 (50)	92 (63)	0.59 (0.06-5.81)	0.650	-	-

Ref – reference category; Firth's bias-corrected logistic regression was performed due to sparse data bias

stabilization (Table 6). Resolution of ICDVT was significantly associated with therapeutic management (Table 7). Patients who underwent anticoagulation had about four times higher odds of resolution than those who underwent conservative management.

DISCUSSION

The clinical characteristics of patients with ICDVT in this population did not substantially differ from previous studies. Despite chronic conditions being identified to be associated more with proximal DVT, the median age of subjects in this study was 70 years, falling within the same range as those in large-scale prospective studies.[10,11] Older patients often have comorbidities and are therefore more likely to undergo multiple diagnostic procedures, such as venous ultrasound, which increased the likelihood of detecting an ICDVT. Also consistent with previous studies,[1,10] there was nearly equal distribution of ICDVT among male and female patients, suggesting no sex predilection for this condition. In contrast, similar with results of previous studies,[1,9,12] the soleal vein was commonly involved (38.4%), indicating a possible predilection of ICDVT in this area.

In this population, the majority underwent venous ultrasound for screening purposes only. Although many of them had risk factors such as inpatient status (132 of 151) and active cancer (58 of 151) that were identified in literature to be contributing to increased risk of DVT,[3,10] only 15 had elevated D-dimer levels, and not all patients were tested. Levels of D-dimers were reported to be significantly lower in patients with ICDVT, reflecting less thrombus burden as compared to proximal DVT.[4]

Table 6. Factors Associated with Stabilization of ICDVT (n=148)

	Stabilization		Logistic regression analysis			
	Yes (n=55) n (%)	**No (n=93) n (%)**	**Crude OR (95% CI)**	***P* value**	**Adjusted OR (95% CI)**	***P* value**
Recent surgery, yes *(Ref: No)*	7 (13)	13 (14)	0.90 (0.33-2.41)	0.830	-	-
Presence of leg varicosities, yes *(Ref: No)*	2 (4)	7 (8)	0.46 (0.09-2.32)	0.349	-	-
Inpatient status, yes *(Ref: No)*	47 (85)	85 (91)	0.55 (0.19-1.57)	0.265	-	-
Active cancer, yes *(Ref: No)*	21 (38)	37 (40)	0.93 (0.47-1.85)	0.847	-	-
Therapeutic Management, Anticoagulation *(Ref: Conservative Management)*	29 (53)	64 (69)	0.51 (0.25-1.01)	0.052	-	-

**Ref – reference category*

Table 7. Factors Associated with Resolution of ICDVT (n=148)

	Resolution		Logistic regression analysis			
	Yes (n=51) n (%)	**No (n=97) n (%)**	**Crude OR (95% CI)**	***P* value**	**Adjusted OR (95% CI)**	***P* value**
Recent surgery, yes *(Ref: No)*	7 (14)	13 (13)	1.03 (0.38-2.76)	0.956	-	-
Presence of leg varicosities, yes *(Ref: No)*	4 (8)	5 (5)	1.57 (0.40-6.11)	0.518	-	-
Inpatient status, yes *(Ref: No)*	44 (86)	88 (91)	0.64 (0.22-1.84)	0.410	-	-
Active cancer, yes *(Ref: No)*	21 (41)	37 (38)	1.14 (0.57-2.27)	0.720	-	-
Therapeutic Management, Anticoagulation *(Ref: Conservative Management)*	41 (80)	52 (54)	3.55 (1.60-7.88)	0.002*	-	-

**Ref – reference category*

In symptomatic subjects, the most common presentation was leg edema, contrary to the study of Heller, et al.,[4] in which it was found that between proximal DVT and ICDVT, the latter was more associated with leg pain and less commonly with edema. Thus, local inflammatory response being more pronounced in the smaller calf veins causing pain may not hold true in all cases. Even so, despite calf veins being multiple in number, thrombus in these areas is sufficient to cause edema.

In a setting where patient population predominantly comprises individuals from higher socioeconomic backgrounds, it seems that there is an inclination to undergo venous ultrasound, often with a lower threshold for its use. While the ACCP guidelines discouraged routine examination of distal veins,[5] the existing protocol for venous ultrasound in our institution includes examination of the entire leg. The reason behind this ACCP recommendation is that ICDVT is unlikely to cause complications if present.[5] This was also demonstrated in the present study where most of the cases had either stabilization or complete resolution of ICDVT. Recurrence was noted in twenty-four (15.89%), proximal DVT extension in sixteen (10.6%) and pulmonary embolism in two (1%) patients.

The risk factors associated with development of ICDVT (ie, recent surgery, presence of leg varicosities, inpatient status and active cancer) as identified in the study of Galanaud, et al.,[3] did not predict outcomes. No significant association with proximal DVT extension, recurrence, development of pulmonary embolism, stabilization or resolution was found. In the study of Elmi, et al., none of the patients who had propagation of

ICDVT had active cancer, although significant relationship was noted between active cancer and development of pulmonary embolism.[2] Similarly, in the present study, despite majority of the subjects having active cancer, none of them developed pulmonary embolism. In the two cases recorded, pulmonary embolism developed around a month after diagnosis of ICDVT. One of the cases had a complicated course during his admission and underwent several surgical procedures which had affected the decision to anticoagulate. The other case of pulmonary embolism had full anticoagulation.

Once diagnosed, ICDVT presents a clinical dilemma in terms of management. The main goal of management is to prevent propagation and pulmonary embolism. Contrary to treatment guidelines on doing surveillance imaging over anticoagulation in patients without high-risk features,[5] majority of subjects (62%) in the present study were anticoagulated either with oral anticoagulant or subcutaneous low-molecular weight heparin. Even so, neither anticoagulation nor conservative management was found to be significantly associated with proximal DVT extension, recurrence and pulmonary embolism. This finding is similar to some studies,[2,11] where composite of propagation and pulmonary embolism only occurred in a minority of patients irrespective of therapy. Therefore, even in the presence of active cancer and inpatient status, which are both cited in the ACCP guidelines to be warranting anticoagulation, management with anticoagulant would not necessarily prevent propagation of ICDVT.

Most studies have focused primarily on the role of anticoagulation in preventing ICDVT propagation, with less emphasis on its effects on stabilization and resolution. In this study, therapeutic anticoagulation was also not significantly associated with stabilization of ICDVT, but was significantly associated with resolution. This contrasts with findings of the CALTHRO study[11] and Shimabukuro, et al.,[13] where most patients achieved complete resolution of thrombosis even without anticoagulation. Based on findings of this study, the role of anticoagulation is in resolving thrombosis rather than preventing complications from its propagation. This implies that withholding anticoagulation may be less of a concern in cases where there are contraindications such as bleeding.

CONCLUSION

This study found that ICDVT had a low incidence of progression, recurrence and development of pulmonary embolism even on surveillance. As demonstrated in this study, previously cited medical risk factors do not play a role in the development of complications in this population. Neither anticoagulation nor conservative management was found to be significantly associated with proximal DVT extension, recurrence and pulmonary embolism, suggesting that ICDVT can safely be managed conservatively. Further studies are warranted to explore more robustly the data on ICDVT to include management and outcomes from other institutions with a wider patient base for social demographics.

Limitations and Recommendations

The present study had several limitations. Being conducted at a single center with a patient population predominantly from higher socioeconomic backgrounds and limited social diversity, the subjects may represent a more selective cohort than the general population with ICDVT, potentially introducing selection bias. Another limitation was due to the retrospective study design. The interval of follow-up from the time of diagnosis of ICDVT varied among subjects which could have reduced the number of events leading to sparse data, although this has been mitigated through Firth's bias-corrected logistic regression. For the outcome of pulmonary embolism, there were only two cases noted. While it was still possible to do regression analysis, the 95% confidence interval was very wide indicating imprecise estimates attributed to low number of patients with outcomes. Furthermore, since information was limited to what was retrievable in chart, the dose and duration of anticoagulation could not always be ascertained. In this study, therapeutic choices also depended on the discretion of the physician. This relevant aspect may be different from other institutions. Lastly, the prevalence of use of antiplatelet and prophylactic dose of anticoagulant agents among this population was not accurately accounted for, undermining the possible role of these medications in clinical outcomes of ICDVT.

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