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Original Article

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Prevalence and Associated Factors of Post-Thrombotic Syndrome in Patients With Deep Vein Thrombosis

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Abstract

Background: Post-thrombotic syndrome (PTS) occurs as a long-term complication of deep vein thrombosis (DVT). The aim of this study was to evaluate the prevalence of PTS and its associated factors in a cohort of patients with lower extremity DVT in Sri Lanka.

Methods: A descriptive cross-sectional study was conducted in 80 patients who were assessed 6 months to 2 years after the acute episode of DVT. They were assessed using Vilalta scale to diagnose and grade the severity of PTS, anthropometry to calculate body mass index (BMI), duplex ultrasound scans, patients' clinic record including international normalized ratio (INR) charts and an interviewer administered questionnaire. Categorical data were analyzed using Chi-square test and continuous variables were analyzed using analysis of variance (ANOVA) to determine association.

Results: Prevalence of PTS was 45.5% (36/80) according to Villalta scale. Recurrent DVT (P = 0.0002), high BMI (P = 0.073), and previous venous in competence (P = 0.032), showed significant association with PTS. Proximal DVT demonstrated a strong association with PTS (P = 0.002). Residual thrombosis at 3 months was strongly associated with PTS (P < 0.001), however, with a bias of very low sample with repeat duplex at 3 months post event. Awareness of PTS was extremely low (n = 0, 0%). Practice of elastic compression stockings (ECSs) use as a preventative measure of PTS failed to show any significant association (P = 0.61).

Conclusions: This study showed a significant prevalence of PTS among patients with previous DVT. Development of PTS is probably multi factorial. A validated risk assessment tool should be used to identify at-risk patients as prevention is the best approach to this irreversible morbidity.

Keywords: Post-thrombotic syndrome; Deep vein thrombosis; Elastic compression stockings

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Introduction

Post-thrombotic syndrome (PTS) is a frequent long-term complication of deep vein thrombosis (DVT). It is defined as a collection of chronic venous symptoms and/or signs secondary to DVT [1].

The reported incidence of PTS varies widely. Various studies have reported different incidence rates for PTS ranging from 20% to 80% following acute DVT [2-4]. However, research done using validated diagnostic criteria estimates it to be as high as 50% despite adequate anticoagulation [4, 5]. Peak incidence of PTS is within the first 1 to 2 years [2], but the cumulative incidence of PTS continues to rise up at 20 years after the initial acute DVT [6]. No incidence or prevalence rates for Sri Lankan population exist to date.

Characteristic signs of PTS include limb edema, perimalleolar or extensive telangiectasia, venous ecstasia, hyper pigmentation, skin indurations and ulceration [7, 8]. In the long run they can develop tender pigmented thickening of the subcutaneous tissue called lipodermatosclerosis. The worst complication of PTS is venous ulceration, which is characteristically chronic, painful, slow to heal and even recurrent [9, 10]. PTS is the commonest cause of venous ulceration [6].

Diagnosis of PTS should only be attempted 3 - 6 months after an acute DVT, when symptoms due to DVT itself are no longer present. Even though there are invasive and noninvasive methods that support the diagnosis, in practice PTS is diagnosed mainly by using simple clinical scores.

There are several clinical scores, which include Widmer scale [11], Villalta scale [12], the Ginsberg measure [13], and CEPA system [14, 15]. Among these Villalta scale and CEPA system take the lead. However, agreement between these scores is poor; and they are not complementary to each other [16].

As an act in standardizing the diagnosis of PTS in clinical studies, subcommittee on control of anticoagulation of the International Society of Thrombosis and Hemostasis (ISTH) has recommended Villalta scale to be used in the diagnosis and grading of PTS [17]. Therefore, Villalta scale is used as the clinical tool in the diagnosis and grading severity of PTS in this study. Villalta scale (Fig. 1) [12] uses five symptoms and six signs as its determinants. Each component is graded (0 - 3) according to severity and the cumulative score is used to diagnose and grade PTS. It can also be used as a binary score to diagnose PTS. Also, it can be used to measure the response to treatment as well [18].

Though it has been recommended by ISTH in the diag-

Symptoms and clinical signs	*None*	*Mild*	*Moderate*	*Severe*
Symptoms				
Pain	0	1	2	3
Cramps	0	1	2	3
Heaviness	0	1	2	3
Paresthesia	0	1	2	3
Pruritus	0	1	2	3
Clinical signs				
Pretibial edema	0	1	2	3
Skin induration	0	1	2	3
Hyperpigmentation	0	1	2	3
Redness	0	1	2	3
Venous ectasia	0	1	2	3
Pain on calf compression	0	1	2	3
Venous ulcer	Absent			Present

Villalta score ≥5 or if venous ulcer present: Villalta score of 5-9 mild, 10-14 moderate, and ≥15 severe.
Modified from Villalta S, Bagatella P, Piccioli A, Lensing AW, Prins MH, Prandoni P. Assessment of validity and reproducibility of a clinical scale for the postthrombotic syndrome [abstract]. Haemostasis 1994;24:158a.

Figure 1. Villalta score.

nosis of PTS, awareness and application of the score in Sri Lankan clinical practice are very limited.

Several risk factors have been shown to be associated with the development of PTS. Various studies have highlighted several factors including sub therapeutic international normalized ratio (INR) [19], proximal thrombosis, higher body mass index (BMI), older age, female sex and previous ipsilateral venous thrombosis [20] as associated risk factors. Residual thrombosis and superficial valvular reflux were also highlighted in one study [21]. Persistently elevated D-dimer levels after initial 3 - 4 months has also been identified as a risk factor in several studies [22, 23].

In the light of current evidence, development of PTS is probably multifactorial and is yet incompletely understood as it is still impossible to accurately predict who will end up with PTS. Unfortunately, PTS has a chronic and progressive disease course. Treatment options for established PTS are limited. Compression stockings and frequent limb elevation are the two mostly practiced methods.

Therefore, the main purpose of this study was to assess the severity and associated factors among patients with DVT attending anticoagulation clinics in two government hospitals in Sri Lanka. By assessing the associated factors and patient awareness we will be able to identify lapses in the knowledge and improve awareness about PTS among patients, clinicians, and healthcare workers in anticoagulation clinics.

The study also looked at the efficacy of elastic compression stockings (ECSs) in preventing PTS in patients following acute DVT.

Materials and Methods

A descriptive cross-sectional study was conducted to determine the prevalence and associated factors of PTS in DVT patients attending anticoagulation clinics in two government hospitals of Sri Lanka.

Clinics included: 1) Professorial unit anticoagulation clinic at Colombo South Teaching Hospital, Sri Lanka; 2) Anticoagulation clinic at Colombo South Teaching Hospital, Sri Lanka (non-professorial units); and 3) Anticoagulation clinic at Colombo North Teaching Hospital, Sri Lanka.

Inclusion criteria

Both male and female patients above 18 years with DVT, after 6 months and less than 2 years of the acute episode were included in this study.

Exclusion criteria

Those who were studied at < 6 months or > 2 years after the acute DVT were excluded.

Eighty (80) patients who fulfilled inclusion criteria were included in the study. Anthropometric measurements (body weight using an electronic scale, height using measuring tape up to the nearest 0.5 cm) were measured. Privacy of the patient

Table 1. Gender Distribution of DVT Patients

	Frequency	Percentage
Male	23	28.8
Female	57	71.2
Total	80	100.0

DVT: deep vein thrombosis.

Table 2. Prevalence of PTS

PTS presence	Frequency	Percentage
No	44	55
Present	36	45
Total	80	100

PTS: post-thrombotic syndrome.

was ensured while obtaining the measurements. Information on duplex ultrasound scan reports at diagnosis and after 3 - 4 months of acute DVT was used to assess residual thrombosis, INR records during the initial 4 months of anticoagulation and D-dimer reports were collected. Each participant was assessed with the Villalta scale to diagnose PTS and its severity. An interviewer-administered questionnaire was used to obtain other necessary information, the demographic details of the person, risk factors, and details of ECS use and awareness of PTS.

Villalta scale (Fig. 1) [12] was applied both as a binary and as a graded scale (0 - 3) to diagnose and determine severity of PTS among the study population. A score of 5 or above was considered diagnostic. Severity was determined using criteria of a score of 5 - 9 as mild PTS, 10 - 14 moderate and 15 or above or presence of a venous ulcer as severe PTS.

Statistical Package for the Social Sciences (SPSS version 23) was used in data analysis. Recorded data were analyzed using paired *t*-test, Chi-square and analysis of variance (ANOVA) to determine association.

Ethical consideration

Ethical approval was taken from the ethical review committee of Colombo South Teaching Hospital, Kalubowila, Sri Lanka. Permission from the directors and consultants of anticoagulation clinics of relevant hospitals was obtained prior to the access. The anonymity and confidentiality of the data and privacy of the patients were secured by using the clinic number without indicating the name of the person. A complete oral explanation regarding the study, its objectives, how the study would be conducted and what would be expected were provided to the participants. The study was conducted in compliance with the ethical standards of the responsible institutions.

Results

Within the study population minimum age recorded was 18 years and the maximum was 74 years, where the majority of them fell within the age group of 45 - 65 years. Mean age of the population was 50.6 years. Majority were females (n = 57, 71.3%) with an approximate male to female ratio of 1: 2.4 (Table 1).

Thirty-six (36) patients (45%) demonstrated the lowest score of 5 or above fulfilling a diagnosis of PTS (Table 2). In the group of diagnosed PTS, majority (n = 28/36, 77.8%) showed mild PTS, five patients had moderate PTS (13.9%) and 8.3% (n = 3) had severe PTS where one patient suffered extreme PTS with debilitating leg ulcers.

Within the study population, recurrent DVT (P = 0.002), higher BMI (P = 0.073) (Table 3) and pre-existing venous incompetence (P = 0.032) demonstrated significant association with PTS. No significant association with gender, age at onset of venous thrombosis or increasing age was noted.

Data also showed a very significant association with residual thrombosis at 3 months (P = 0.001), however, with an associated bias of a very low sample number with a repeat scan at 3 months.

Further, thrombosis in proximal deep veins demonstrated a strong association with PTS (P = 0.002) where 29 (80.6%) patients diagnosed with PTS within the study population being with post-proximal DVT (Table 4). Only seven patients (19.4%) were with post-distal DVT. This observation correlated well with the higher prevalence of PTS (n = 29, 59.2%) among patients who had preceding proximal DVT, and a low prevalence of PTS (n = 7, 22.6%) in those with the distal DVT within the study population. There was no significant association of PTS with unprovoked DVT (Table 5).

Sub therapeutic anticoagulation during the initial face of a DVT was not analyzed as an associated factor for PTS due to lack of consistent follow-up INR recordings on patient records. D-dimer tests were hardly done across all three clinics.

Unfortunately, awareness of this clinical syndrome as a possible long-term complication of DVT was extremely low among the study population (n = 0).

ECS usage post DVT showed significant variation among patients especially the type of ECS, duration they wore during the day and consistency of the practice over the period largely varied. Data obtained were categorized in to three groups, never, less than 6/12 or occasionally or more than 6/12 or regularly (Table 6). Cross analysis of these groups failed to show significant association of use of ECS as a preventive measure (P = 0.61), however with the caveat of observed extreme variable use of ECS and patient bias.

Discussion

Prevalence of PTS among the study population was 45%, in keeping with available prevalence data of about 50% from studies done using validated diagnostic criteria [4, 5]. Majority demonstrated mild PTS and 8.3% had severe PTS. Though these rates cannot be directly applied to general population, they reflect a significant disease burden among the post thrombotic patient group in Sri Lanka.

Recurrent DVT, higher BMI, pre-existing venous incompetence, and proximal site of DVT demonstrated a significant association with PTS.

Table 3. Association With Age and BMI

	N	Mean	SD	SE	95% CI for mean		Minimum
					Lower bound	Upper bound	
Age							
No	44	49.56	14.403	2.196	45.13	53.99	18
Present	36	52.06	12.860	2.143	47.70	56.41	22
Total	80	50.7	13.692	1.540	47.63	53.76	18
Income							
No	22	26,454.55	9,698.931	2,067.819	22,154.28	30,754.81	6,000
Present	14	30,857.14	13,427.052	3,588.530	23,104.59	38,609.69	7,000
Total	36	28,166.67	11,320.020	1,886.670	24,336.52	31,996.81	6,000
Age at onset							
No	44	45.37	15.846	2.416	40.50	50.25	16
Present	36	47.03	13.995	2.366	42.22	51.84	19
Total	80	46.12	14.971	1.695	42.74	49.49	16
BMI							
No	44	24.426	4.2971	0.6553	23.103	25.748	17.6
Present	36	26.449	5.5353	0.9356	24.547	28.350	18.2
Total	80	25.333	4.9625	0.5619	24.214	26.452	17.6

SD: standard deviation; SE: standard error; CI: confidence interval; BMI: body mass index.

No significant association with gender, age at onset of venous thrombosis or increasing age was noted. Data also showed a very significant association with residual thrombosis at 3 months. These findings were in keeping with current available studies.

A prospective multicenter cohort study done by Khan et al in 387 outpatients and inpatients revealed that venous thrombosis of the common femoral or iliac vein (2.23 increase in score vs. distal (calf) venous thrombosis; $P < 0.001$), higher BMI (0.14 increase in score per kg/m^2; $P < 0.001$), previous ipsilateral venous thrombosis (1.78 increase in score; $P = 0.001$) and older age (0.30 increase in score per 10-year age increase; $P = 0.011$) were significant additional predictors of PTS over the time [20]. Female sex was inconsistently associated with PTS [20, 22].

A prospective study on 111 patients with a diagnosis of DVT of the lower limb looked at noninvasive radiological predictors of PTS. Presence of thrombosis in proximal veins at diagnosis had a higher risk compared with distal thrombosis (risk ratio (RR): 2.3%, 95% confidence interval (CI): 1.0 - 5.6). PTS was diagnosed in 62% of patients with residual thrombosis in the proximal veins after an interval of 6 weeks following DVT, leading to a 1.6-fold increased risk (95% CI: 1.0 - 2.5). Valvular reflux in the superficial veins at 6 weeks following DVT was a predictor with a 1.6-fold increased risk as compared to those without superficial reflux (95% CI: 1.1 - 2.3). The study concluded that age over 50 years, proximal localization of the

Table 4. Site vs. PTS Presence

	PTS presence	
	No	Present
Site		
Distal	24	7
Proximal	20	29
Total	44	36

P value = 0.002. PTS: post-thrombotic syndrome.

Table 5. Nature of DVT vs. PTS Presence

	PTS presence	
	No	Present
Nature of DVT		
Unprovoked	27	28
Provoked	17	8
Total	44	36

P = 0.14. DVT: deep vein thrombosis; PTS: post-thrombotic syndrome.

Table 6. Stockings vs. PTS presence

	PTS presence	
	No	Present
Stockings		
Never	25	17
Less than 6/12 or occasionally	11	11
More than 6/12 or regularly	8	8
Total	44	36

P value = 0.61. PTS: post-thrombotic syndrome.

thrombus at entry, residual proximal thrombosis and superficial valvular reflux at 6 weeks as leading risk factors of PTS in patients with a first episode of DVT. Also, it concluded that duplex scanning after 6 weeks of acute DVT to be an important noninvasive radiological method that can be used for the detection of patients at risk of PTS early [21]. Presence of superficial venous incompetence/varicose veins acts as an independent predictor of subsequent PTS development [24, 25].

As with any health hazard, raising awareness among at-risk group and healthcare professionals plays an important role in prevention of PTS. Unfortunately, knowledge of this clinical syndrome as a possible long-term complication of DVT was extremely low among the study population. PTS-related symptoms get worse on standing and walking. This brings about a major impact on activities of daily living and quality of life of these patients [26-29].

ECSs reduce venous hypertension, improve venous reflux, and thus improve microcirculation [30]. A meta-analysis of two historic studies on the role of ECSs/graduated compression stockings (GCSs) in prevention of PTS; Pradoni et al [31] and Ginsberg et al [32] concluded that sustained use of ECS following a DVT to be effective in lowering the risk of PTS. However, SOX trial, a Canadian multicenter double-blinded placebo-controlled trial of ECS efficacy in preventing PTS studied 806 patients (410 patients were randomly assigned to active ECS and 396 to placebo ECS). The cumulative incidence of PTS was 14.2% in active ECS versus 12.7% in placebo ECS (hazard ratio adjusted for center: 1.13, 95% CI: 0.73 - 1.76; P = 0.58). The study concluded that ECS did not prevent PTS after first proximal DVT [33]. In accordance, ACCP guidelines on anti-thrombotic therapy and prevention of thrombosis (2016 revision) no longer recommends the routine use of ECS for the prevention of PTS in patients with DVT [34]. In the study conducted by Kahn et al, a comparison between Villalta scale and other score systems showed that the proportion of patients labeled as having PTS (37%) was nearly five times more than that with Ginsberg measure, indicating that Ginsberg has a tendency to overlook mild PTS [35]. SOX trial used Ginsberg criteria to diagnose PTS which could have overlooked mild cases of PTS, which would possibly explain the wide variation of study out comes on this setting. Determination of the role of ECS in unselected/high-risk patient groups would provide a better understanding on its role in PTS prevention.

We were unable to reliably conclude on the role of ECS as a preventative method of PTS given the wide variation of its use among the study population; however, it was apparent that use of ECS in this setting to be less practical and poorly adhered by the patient.

Conclusions

The study showed a significant prevalence of PTS among patients with previous DVT. High BMI, proximal site of the DVT, residual thrombosis and pre-existing venous incompetence demonstrated a significant association with PTS. In the light of current evidence, development of PTS is probably multifactorial, and the awareness of this debilitating long-term complication of DVT appears to be extremely low among patients. There is clearly a hidden but significant health care and socio-economic burden associated with PTS.

A validated risk assessment tool should be used to identify at-risk patients as prevention appears to be the best approach to this irreversible morbidity. SOX-PTS score, an externally validated clinical score should be incorporated into the initial assessment to identify at-risk patients. Raising awareness and modifying risk factors associated with PTS should be emphasized and should be made an essential aspect in DVT management to improve long-term outcomes.

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Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

Informed written consent was obtained from each participant before the commencement of the study.

Author Contributions

SA wrote the proposal, managed the literature survey, carried out the data collection, performed data analysis and wrote the first draft of the manuscript. IW and CK designed the study, corrected the proposal and literature survey, supervised and guided methodology and data analysis and corrected and modified the manuscript. All the authors read and approved the final version of the manuscript.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

Abbreviations

PTS: post-thrombotic syndrome; DVT: deep vein thrombosis; BMI: body mass index; ISTH: International Society of Thrombosis and Hemostasis; ECS: elastic compression stocking

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