A STUDY OF CLINICAL SPECTRUM OF POST PHLEBITIC LEG

Dissertation Submitted To

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI – 600032

With partial fulfilment of the requirement

for the award of degree of

M.S. DEGREE IN GENERAL SURGERY
BRANCH – I

Register Number: 221711205

THANJAVUR MEDICAL COLLEGE AND HOSPITAL

THANJAVUR

MAY– 2020

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This is to certify that the dissertation entitled "**CLINICAL SPECTRUM OF POST PHLEBITIC LEG**" submitted by DR.P. KARTHICK appearing for M.S. GENERAL SURGERY BRANCH I DEGREE EXAMINATION in MAY 2020 is a bonafide record of work done by him under my direct guidance and supervision in partial fulfilment of regulations of The **Tamilnadu Dr. M.G.R. Medical University, Chennai.** I forward this to The **Tamilnadu Dr. M.G.R. Medical University, Chennai.**

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CLINICAL SPECTRUM – POST PHLEBITIS LEG

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Dept. of GENERAL SURGERY **Thanjavur Medical College, Thanjvur**

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DECLARATION

I solemnly declare that this dissertation entitled "**CLINICAL SPECTRUM OF POST PHLEBITIC LEG**" is a record of workdone by me in the department of General Surgery, Thanjavur medical college, Thanjavur, during my Post Graduate Course from 2017-2020 under the guidance and supervision of my unit Chief **Prof. DR.K.SATHYABAMA, M.S,.** It is submitted in partial fulfilment for the award of **M.S. DEGREE EXAMINATION- BRANCH I (GENERAL SURGERY)** to be held in **MAY 2020** under The **Tamilnadu Dr. M.G.R. Medical University, Chennai.** This record of work has not been submitted previously by me for the award of any degree or diploma from any other university.

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DATE:

ACKNOWLEDGEMENT

I express my extreme gratitude to **Prof. Dr. K. SATHYABAMA M.S.,**

Head of the Department of Surgery, for her constant guidance and suggestions throughout my study period.

I express my extreme gratitude to **Prof. Dr. S.MARUTHUDURAI M.S., Mch,**

Head of the Department of Vascular Surgery, for his valuable guidance and encouragement during my study period.

I express my profound gratitude to **Dr. S. JEEVARAMAN M.S.D.L.O** for his valuable help and guidance during my study.

I express my profound gratitude to **Dr. F. GREY BERNARD M.S,**

Dr. S.KARTHIKEYAN M.S, DR. P.MOHANRAJ M.S. Mch (Vascular surgery), for their valuable guidance and encouragement.

I am very thankful to All Assistant professor of general surgery and vascular surgery for their valuable help and suggestions.

I express my sincere thanks to all patients, who in spite of their physical and mental sufferings have co-operated and obliged to my request for regular follow up, without whom my study would not have been possible.

ABBREVIATIONS

PTS	Post thrombotic syndrome
QOL	Quality of life
DVT	Deep vein thrombosis
HRQoL	Health related quality of life
CEAP	Clinical, Etio-pathological, Anatomical, Pathology
EVLA	Endo-venous laser ablation
CDT	Catheter directed thrombolysis
ISTH	International society of thrombosis & haemostasis
BMI	Body mass index
RFA	Radio-frequency ablation
DOAC	Direct oral anti coagulants
PE	Pulmonary embolism
UE	Upper extremity
LE	Lower extremity
USG	Ultrasonography
VTE	Venous thromboembolism
CVI	Chronic venous insufficiency
RCT	Randomised control trials
ECS	Elastic compression stockings
LMWH	Low molecular weight heparin
VKA	Vitamin k antagonist
PEVI	Percutaneous endo vascular intervention

CONTENTS

INTRODUCTION

Post thrombotic syndrome (PTS) is a common chronic complication of deep vein thrombosis of the leg (DVT). Treatment options are limited therefore emphasis is placed on its prevention. Several risk factors have been recognized, but were so far not used for risk stratification or translation into prediction models. Early interventions did not yet result in more successful preventive treatment strategies; for the acute phase of DVT there is equipoise on the value of elastic compression, as well as on catheter directed thrombolysis. There are no drugs specifically targeted at PTS prevention. The use of anticoagulant medications such as direct oral anticoagulants (DOACs) might decrease PTS incidence, but this needs to be corroborated. Both research into more effective treatment options as well as future PTS management may benefit from a nuniform diagnostic strategy and the use of prediction rules to better allocate treatment and thereby increase treatment efficacy.

HISTORY

The first case of DVT affecting the lower limb in an adult, Raoul, was reported in 1271 AC by Guillaume de Saint- Pathus.

In the late 1600s, Richard Wiseman, was believed to have postulated the phenomenon of VTE which was secondary to “coagulation of the serum”. From

early 1700s up to the mid-1800s, there was an interpretation that a thrombus was, an inflammatory process associated with the presence of pus (the manifestation of phlebitis).

In the year 1850, Rudolph Virchow,had his enormous contribution to the field of thrombosis.

The current consensus of VTE as a multifactorial disease and classified its multiple risk factors under 3 main components: stasis of blood, damage to the vessel wall, and hypercoagulability. Although these components as the causes of venous thrombosis were classically referred to as the “Virchow’s triad”.

Subsequent scientific advances led investigators to weigh the specific contribution of each of the inter-related triad components to the development of VTE.

Whereas initially vein wall damage was thought to be less important, the re-discovered interrelation between thrombosis and inflammation – in its modern sense - gave a new meaning to the role of the vessel wall in the aetiology of VTE.

New findings indicate that inflammation or local damage can modify the endothelial surface from non-thrombogenic to pro-thrombotic. Inflammation has a prominent role in the development of PTS.

Nearly 20–50% of patients with a deep venous thrombosis (DVT) develops post-thrombotic syndrome (PTS), within 2 years duration, despite treatment with

anticoagulation. The pathophysiology is complex. Outflow obstruction & reflux by valvular incompetence leads to chronic venous hypertension which appear to play a major role in the development of PTS.

Villalta scoring system, as recommended by the current guidelines, is mainly used in the diagnosis of PTS. It should be deferred forabout 3 to 6months after an acute phase when pain & swelling associated with acute DVT have resolved. Patients present with a variety of spectrum of symptoms and signs of chronic venous insufficiency such as pain, feeling of heaviness, oedema, paraesthesia's, skin pigmentation and in late stages with venous ulceration.

Studies implicates older age, obesity (BMI>30kg/m2), proximal DVT and recurrent DVT as risk factors for PTS. Management of venous ulcers is a challenge for a patient and healthcare system, given their recurrences in 26–69% of patients within 12 months. This study is aimed at evaluation of 0 to 1 year PTS cumulative incidence in patients diagnosed with a first DVT, and to determine how these symptoms and signs evolved over time & how many patients with PTS either improved/ worsened or continued to remain the same.

The clinical presentation of post thrombotic syndrome (PTS) is characterized by oedema and skin changes such as venous ectasia, varicose veins, redness, eczema, hyperpigmentation, and in severe cases fibrosis of the subcutaneous adipose tissue. This condition, known as lipo-dermatosclerosis

results in impaired skin perfusion and poses patients at an increased risk of venous ulceration. Venous ulceration is the ultimate and most severe presentation of PTS.

In addition to this array of skin problems, patients may experience leg symptoms such as heaviness, pain, itching, cramps, and paraesthesia, with a symptom pattern that is worse with activity (standing, walking) and better with rest (elevation of the leg).

Some patients experience “bursting” pain upon exercise, known as venous claudication. This is a result of venous outflow restriction, which is most often situated in the iliofemoral tract. Post thrombotic syndrome is an independent determinant of health- related quality of life (HRQoL) with a differential decrease in quality of life associated with disease severity.

Also, variations in patients’ or disease characteristics may impact HRQoL differently. The “disease” specific VEINES- QoL is influenced by a variety of patient factors such as co morbidity (Charlson score), gender, age, and obesity. Both PTS and obesity (BMI > 30/m2) were found to be independently associated with impaired HRQoL with a five to seven times larger impact for PTS.

Post thrombotic syndrome is a chronic condition that is diagnosed based on a clinical score. Although not all symptoms and signs are irreversible once PTS is diagnosed this diagnosis is deemed permanent. There is no gold standard for the diagnosis of PTS and there might not ever be one, as PTS is a syndrome

and thus a combination of patient reported symptoms and physician assessed physical signs.

The choice for a clinical score incorporating these features may therefore be the best option. This is even more so when it is considered that a large proportion of the disease burden is formed by the impact on HRQoL. Just objectifying lesions by imaging techniques or measuring ambulant venous pressure will not encompass the impact of the condition but may be used as confirmation and tool to assist in allocation of different treatment modalities. Post thrombotic syndrome not a rare condition, occurring in about 20%- 50% of patients.

Plurality of diagnostic scoring systems may be a likely contributor to the lack of precision in the reported prevalence and incidence of the condition. There are at least six scores that have been used in the recent past, and some of them are still being used today: the more or less PTS- specific scores by Villalta, Brandjes, and Ginsberg, as well as the scores that were intended for the classification of venous disease: the VCSS, CEAP, and Widmer score.

None of the so- called “PTS- specific” scores have been formally validated. It is remarkable that the incidence of PTS appears not to have changed over the years, in spite of many improvements in the management of acute DVT, including better anticoagulation, early mobilization, and adequate compression therapy when needed.

EPIDEMIOLOGY:

According to estimates, PTS affects 15 to 50% of adults diagnosed with LE DVT, and is clinically significant in 10-15% of cases. The mean frequency of UE PTS in adults is 15% (range: 7-46%).

The variability of PTS frequency reported in adults is due to the different criteria used to define PTS. In fact, one study found that the frequency of LE PTS in 124 adult patients examined by a single rater using four classification systems (Widmer criteria, Venous Clinical Severity Score, Villalta Scale, and Brandjes criteria) ranged between 31% and 66%.

UE PTS has been less studied and reported in adults, in view of the much lower frequency of UE DVT. Whereas approximately 95% of DVT in adults occur in the LE, only 5% involve the UE.

ANATOMY:

The anatomy of the arterial system is relatively constant but thatof venous system is subject to individual variation. In the lower limb superficial veins carry only about 10% of blood whereas remaining passes via deep veins. Superficial veins lie superficial to muscle and fascia of the limb. All veins contain valves every few centimetres, which ensures that blood flows towards the heart.

THE VENOUS SYSTEM:

The veins may be divided into 3 main systems.

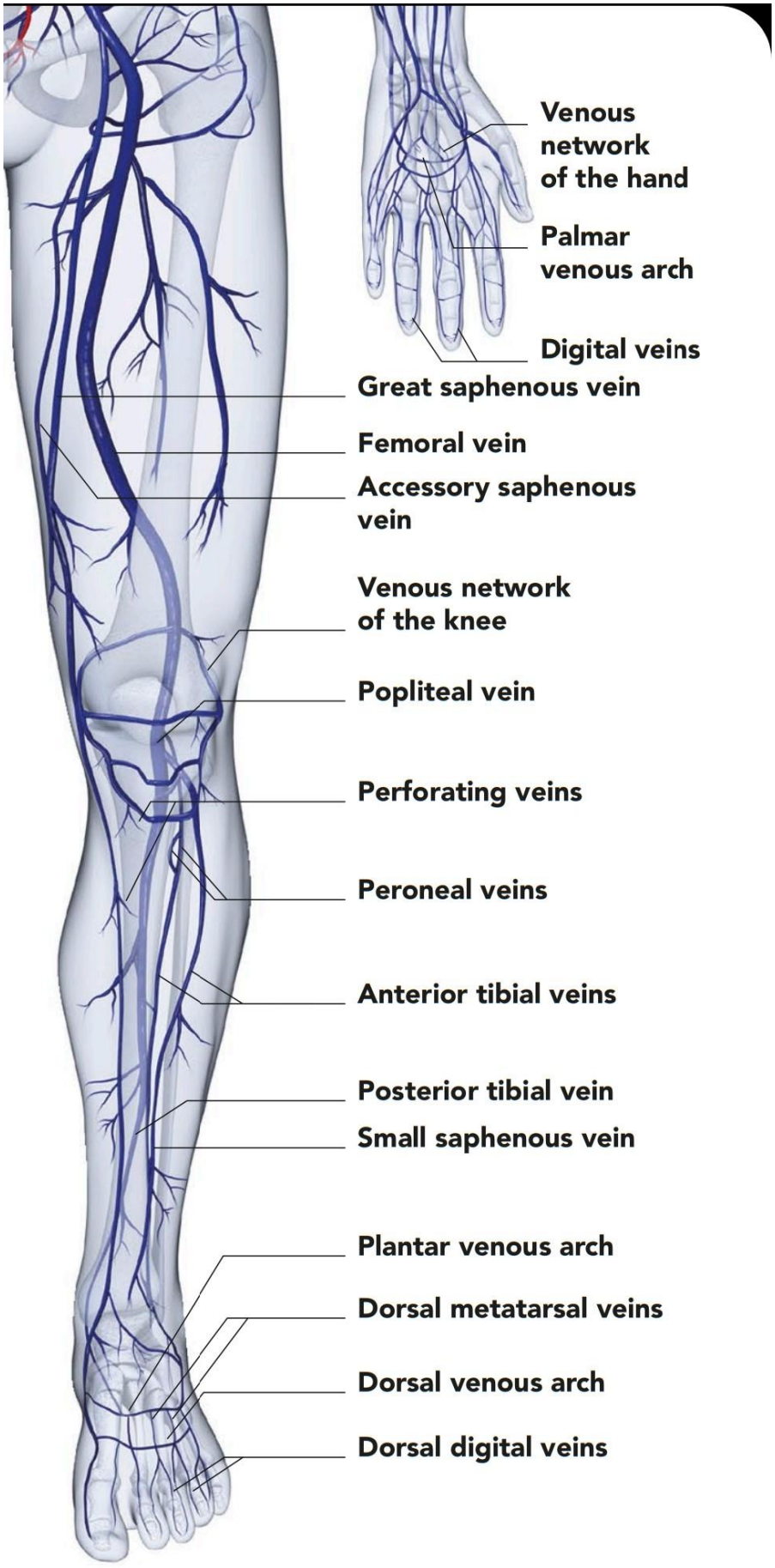
a. The superficial system

b. The perforator system

c. The deep system

The superficial veins are underneath the skin, in the subcutaneoustissue. The deep veins accompany the arteries. Valves are present in both systems, but are more numerous in the deep veins.

THE SUPERFICIAL SYSTEM: - The superficial system of the leg consists of two major veins and their tributaries, namely the long and short saphenous


Venous network of the hand
Palmar venous arch
Digital veins
Great saphenous vein
Femoral vein
Accessory saphenous vein
Venous network of the knee
Popliteal vein
Perforating veins
Peroneal veins
Anterior tibial veins
Posterior tibial vein
Small saphenous vein
Plantar venous arch
Dorsal metatarsal veins
Dorsal venous arch
Dorsal digital veins

veins. They lie superficial to deep fascia. They are thick walled because of the presence of smooth muscle and some fibrous and elastic tissues in their walls. Valves are numerous in the distal parts of these veins than their proximal parts. A large proportion of their blood is drained into deep veins through perforating veins.

DEEP VEIN: -

The deep veins accompany the major arteries and their branches and are usually paired. They contain valves to prevent reflux of blood distally.

Deep veins are,

- Medial & Lateral plantar
- Dorsalis pedis
- Anterior & Posterior Tibial
- Peroneal
- Popliteal and femoral veins and their tributaries.

They are surrounded by powerful surrounding muscles. The valves are numerous in the deep veins than in the superficial veins. They are more efficient channels than superficial veins because of the driving force of muscular contraction.

PERFORATORS: -

The superficial and deep veins are connected by perforator veins. They have

valves which permit only unidirectional flow of blood from superficial to deep veins. They are mentioned below.

Indirect Perforating veins: -

These veins connect the superficial with the deep veins through the muscular veins.

Direct Perforating veins: -

These will connect the superficial veins directly to deep veins. There are about five perforators along the great saphenous vein and one along the small saphenous vein.

The small direct perforating veins are follows

1. In the Thigh: - The Adductor canal Perforator connects the great saphenous vein with the femoral vein in the lower part of the adductor canal.

2. Below the Knee: -One Perforator connects the great saphenous vein or the posterior arch veins with the posterior tibial vein.

3. In the Leg: -A lateral perforator is present at the junction of the middle and lower thirds of the leg.it connects the small saphenous vein or one of its tributaries with peroneal vein.

Medially there are three perforators which connect the posterior arch vein with

the posterior tibial vein.

a) The upper medical perforator lies at the junction of the middle and lower thirds of the leg.

b) The Middle medical perforator lies above the medical malleolus.

c) The Lower medial perforator lies in the posteroinferior to the medial malleolus.

PHYSIOLOGY OF THE VEINS OF LOWER LIMB

As might be expected the leg veins are thicker walled and possess a greater development of adventitial connective tissue than elsewhere.

Such structural modifications seem to be related to the gravitationalstresses which these leg veins have to endure.

1. The superficial veins have smooth muscle in their walls and thedeep veins do not have making them more or less passive reservoir of blood. Whereas superficial veins contract in response to directstimuli and other stimulus like cold, warm, and drugs.

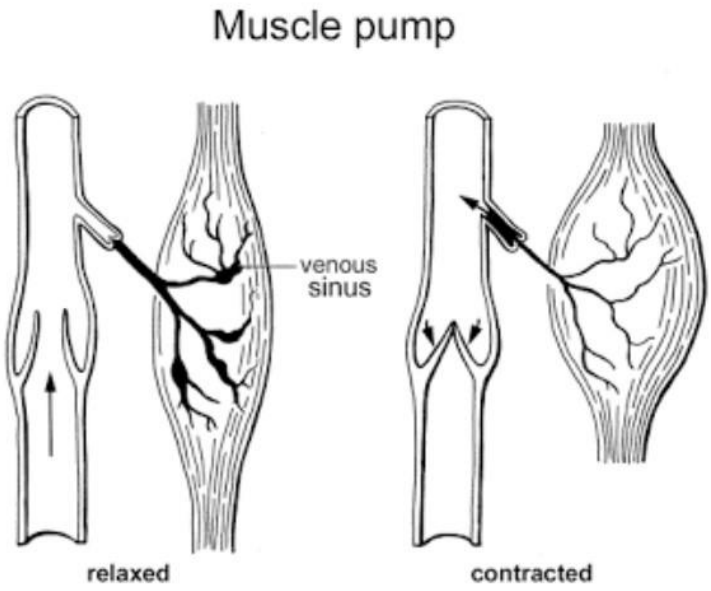
2. The physiology of venous return from the leg is quite differentwhen lying prone and when standing up. By the time it emerges from the capillaries it is at low pressure (about 20mmHg), but thisis enough for the blood to return to the heart.

Following factors help in venous return

1. Negative pressure in the thorax.

2. The calf muscle pump.

3. Competent valves.



Venous sinuses: effect of contraction of calf muscle

HEMODYNAMICS IN THE VENOUS CIRCULATION

Venous return from the LE in the standing position is accomplished by the action of venous valves, the peripheral muscle pumps (foot, calf, and thigh), and a small effect of the gradient in dynamic pressure generated by the heart. These mechanisms are able to work against gravity and offset hydrostatic pressure returning the blood from the periphery to the heart, preventing reflux and fluid accumulation. The peripheral calf pump in conjunction with normal venous

valves constitute the most efficient mechanism for blood return, and their combined action decreases venous pressure in the leg during walking.

In contrast, venous return in the UE is mainly regulated by the dynamic pressure gradient generated by cardiac pumping, and the peripheral muscle pump does not play a significant role. In addition, there are fewer valves in the UE than in the LE, and they are less relevant to the physiology of the UE than the valves in the LE.

These physiologic differences have a major impact on the pathophysiology of PTS and, consequently, on the development of the signs and symptoms we attempt to measure, and will be further explained later on this chapter.

PATHOPHYSIOLOGY

A).**Macroscopiclevel**: LE PTS is a form of secondary chronic venous insufficiency (CVI), characterized by persistent flow obstruction and valvular reflux.

The relevance of the combined role of both these components was only understood after a series of seminal studies conducted in the early 1990s by Strandness et al, the same investigators who revolutionized the field of vascular imaging by introducing the use of Doppler ultrasound, as mentioned earlier. The work of these researchers advanced the then existing notion that centered the

pathophysiology of PTS on valvular reflux alone. As with the development of knowledge on VTE pathophysiology, subsequent studies weighed the role of residual obstruction differently, suggesting it may even have a more prominent role than valvular reflux.

The combination of obstruction and valvular reflux can result in sustained elevation of venouspressure (venous hypertension) and changes in shear stress affecting the surface of endothelial cells, which in turn lead to a diverse array of clinical manifestations seen in LE PTS, such as oedema, skin inflammation, skin induration, skin pigmentation, and venous ulcers.

The pathophysiology of UE PTS is far less understood. Valvular function does not appear to have a prominent role in PTS affecting this territory, which may explain why certain clinical features of LE PTS are not seen in UE PTS, as discussed later.

B). **Microscopic level**: The pathophysiology of PTS is tightly dependent on the relation between the orchestrated inflammatory response observed in the context of DVT and thrombus resolution.

During the acute DVT phase, the thrombus reduces blood flow and stretches the endothelium, inducing hypoxia, inflammation, and migration of inflammatory cells to the perivasculature.

Neutrophil and subsequent monocyte infiltration following acute DVT promotes thrombus resolution and organization. However, both inflammation and recanalization can also result in vein wall injury and valvular reflux by mechanisms not entirely understood, probably related to the release of growth factors, proteinases, and cytokines.

Venous hypertension, the hallmark of all forms of CVI, develops in the chronic DVT phases as a consequence of inadequate vessel recanalization, impaired fibrinolysis, and vein wall stiffness, which result in the ongoing venous flow obstruction described in the previous section.

Animal studies have shown that sustained elevated venous pressure results in inflammation and valve remodelling, with loss of function.

Venous hypertension can cause endothelial glycocalyx shedding with endothelial cell activation. Activated endothelial cells expose adhesion molecules to leukocytes, release cytokines, and express pro-coagulant, pro-migration, pro-apoptotic, and pro-growth genes.

Attracted leukocytes migrate and infiltrate the sub-endothelial extra cellular matrix, where they further amplify the inflammatory response by releasing cytokines. This cascade of events triggers chronic inflammatory injury, alteration in capillary perfusion, interstitial accumulation of degradative enzymes, immune host reaction, and alteration of wound healing and/or of tissue remodelling.

These events are thought to lead to the myriad of signs and symptoms characteristic of PTS.

Normally, the venous flow is determined by the venous pump which is defined as the pumping effect of leg muscles on venous flow and by the venous valves which are bicuspid structures that direct blood flow in a unidirectional fashion from distal to proximal veins and from the superficial to the deep venous system.

PTS occurs due to a combination of mechanisms including venous outflow obstruction, destruction of the venous valvular apparatus, development of venous reflux, calf muscle pump dysfunction, and reduced wall shear stress which triggers an inflammatory process within the involved vein.

These mechanisms result in elevated venous pressures in the affected limb particularly in an upright position, and can worsen venous reflux resulting in a vicious cycle of events.

The exact pathogenesis of PTS is not completely understood. The limited ability to quantify the venous obstruction and venous valvular reflux has resulted in conflicting.

Literature on whether PTS development is mainly a consequence of outflow obstruction, valvular incompetence, or both. After an episode of acute

proximal DVT, patients with venous obstruction persisting for the first 3 to 6 months were reported to be at increased risk for developing PTS.

However, other studies have disputed the importance of persistent venous obstruction and suggested that the presence of venous reflux was more likely to contribute to the development of PTS. Calf muscle pump dysfunction may also be involved in the late onset of PTS because it takes more than 2 years post-DVT for the damage to involve muscle tissues.

Ultimately, the end result of persistent venous obstruction and worsening valvular reflux results in the development of ambulatory venous hypertension. In such a situation, the ambulatory venous pressures can reach up to 60 to 90 mmHg which subsequently promotes venous distention and further valve incompetence. Incompetent valves lead to sluggish proximalblood flow.

As a result, the superficial and deep veins become more distended and the venous hypertension worsens, which further damages the valves. When the superficial veins become maximally distended, only a small volume of refluxed blood through the incompetent valves is required to produce a large increase in pressure which leads to third spacing and tissue oedema.

After acute DVT, the evolution of the thrombus is a dynamic process. Neutrophil and monocyte chemo-attractants, such as pro-inflammatory proangiogenic interleukin-8, are released and stimulate the release of vascular

endothelial growth factor and basic fibro-blast growth factor, which then regulates the formation of neo-vascular channels within the thrombus.

However, the resultant recanalization is usually incomplete, resulting in residual ambulatory venous hypertension. It has been shown that even after the use of anticoagulation, residual venous thrombosis persists in many patients, which is capable of initiating the anatomic, and histologic changes associated with chronic venous insufficiency and then the development of PTS.

Low wall shear stress stimulates the adhesion of leukocytes to the capillary endothelium and trans-endothelial migration resulting in perivascular leucocyte stasis and inflammation. The inflammation increases capillary permeability resulting in capillary leakageand lowerextremity oedema. The exact mechanism by which low wall shear stress stimulates these inflammatory events is not well understood.

Pain is a major symptom of PTS and is stimulated by pro-inflammatory mediators which activate the nociceptors located within the venous walls. Moreover, as leukocytes adhere to the vein walls, they become activated and release inflammatory cytokines which contribute to further valvular damage. This promotes worsening of the cycle of reflux and elevated venous pressure.

RISK FACTORS AND BIOMARKERS

Several studies investigated the risk factors lead to the development of PTS. They include clinical, radiological and inflammatory biomarkers that predict progression to PTS inDVT patients.

Both obesity (BMI $\geq$ 30) and contralateral limb ectasia increases the risk ofhaving PTS 2-fold. A sub-therapeutic INR for more than 20% of the time during the first 3months of warfarin therapy was significantly associated with increased risk of developing PTS.

Sex, ethnicity and combination of DVT and PE versus DVT alone did not alter the risk of PTS.

Proximal DVT (iliac, femoral and popliteal vein) is a strong predictor for developing PTS. This is likely related to the involvement of the profunda femoral vein in proximal thrombosis which impairs the development of collateral channels and worsens the underlying pathophysiological mechanisms described above.

Moreover, involvement of the common femoral vein impairs drainage from the lower extremity resulting in severe DVT symptoms and PTS. On long term follow up, patients with proximal DVTs were found to have greater residual vein thrombosis and deep venous reflux compared to patients with distal DVTs.

In addition, the thrombus recanalization rate was found to be muchlower for ilio-femoral DVT compared to distal DVT.

Radiological risk factors for developing PTS based on ultrasound include the following:

“Extensive clot load on presentation; clot regression at 6 months not exceeding 50%; venousfilling index exceeding 2.5 ml/s; and abnormal outflow rate measured by a 2 second maximum outflow volume (<60% of the volume depleted after 2 seconds). Patients with 3 or more of theabove-mentioned ultrasound findings had a significant risk of developing PTS with a sensitivity of 100%, specificity of 83%, and positive predictive value of 67%”.

Moreover, residual thrombus and deep venous reflux increased the risk for PTS. Johnson et al reported that on 6 months follow-up ultrasound of patients with DVT, 65% of cases were found to have both obstruction and venous reflux and were 3.5 times more likely to develop PTS compared to patients without obstruction and reflux.

Underlying hypercoagulable states may contribute to the development of PTS, as shown by a recent prospective study that revealed an independent association between F VIII activity and PTS with an odds ratio of 2.83 (95% confidence interval, 1.09-7.42; P= 0.034).

Studies havealso suggested a strong relationship between inflammation and thrombosis. For example, Shbaklo et al observed increased levels of intracellular adhesion molecules-1 (ICAM) and interleukin 6(IL-6) in patients who develop PTS and a recent systemic review similarly showed significant correlations between ICAM and PTS.

In addition, several studies have also shown an association between c-reactive protein (CRP), IL 6, IL8, IL10 and ICAM and the development of PTS, however the results have not been consistent.

Although inflammatory biomarkers associated with PTS are currently under investigation, PTS is still a clinical diagnosis and the value of measuring these markers is still not clear and is not currently utilized in routine clinical practice.

CLINICAL PRESENTATION AND DIAGNOSIS:

Patients who develop PTS commonly report pain and swelling of the affected limb, especially after prolonged standing or walking, which eventually improves with rest or raising the leg. In addition, they might complain of lower extremity muscle cramping at night, itchiness or heaviness. Advanced cases of PTS usually present with an ulcer on the affected leg.

LACK OF GOLD STANDARD FOR THE DIAGNOSIS

At the International Society on Thrombosis and Haemostasis (ISTH) subcommittee meeting in 2008 consensus was reached to establish the diagnosis of PTS on a single Villalta score ≥5, at least 6 months after the acute event of DVT (ISTH consensus scoring method).

The Villalta scale has many advantages, as it has good measurement properties and it is easy to apply. The Villalta score combined with a venous disease–specific quality- of- life questionnaire to standardize the subjective criteria was even suggested as the "gold" standard for the diagnosis of PTS.

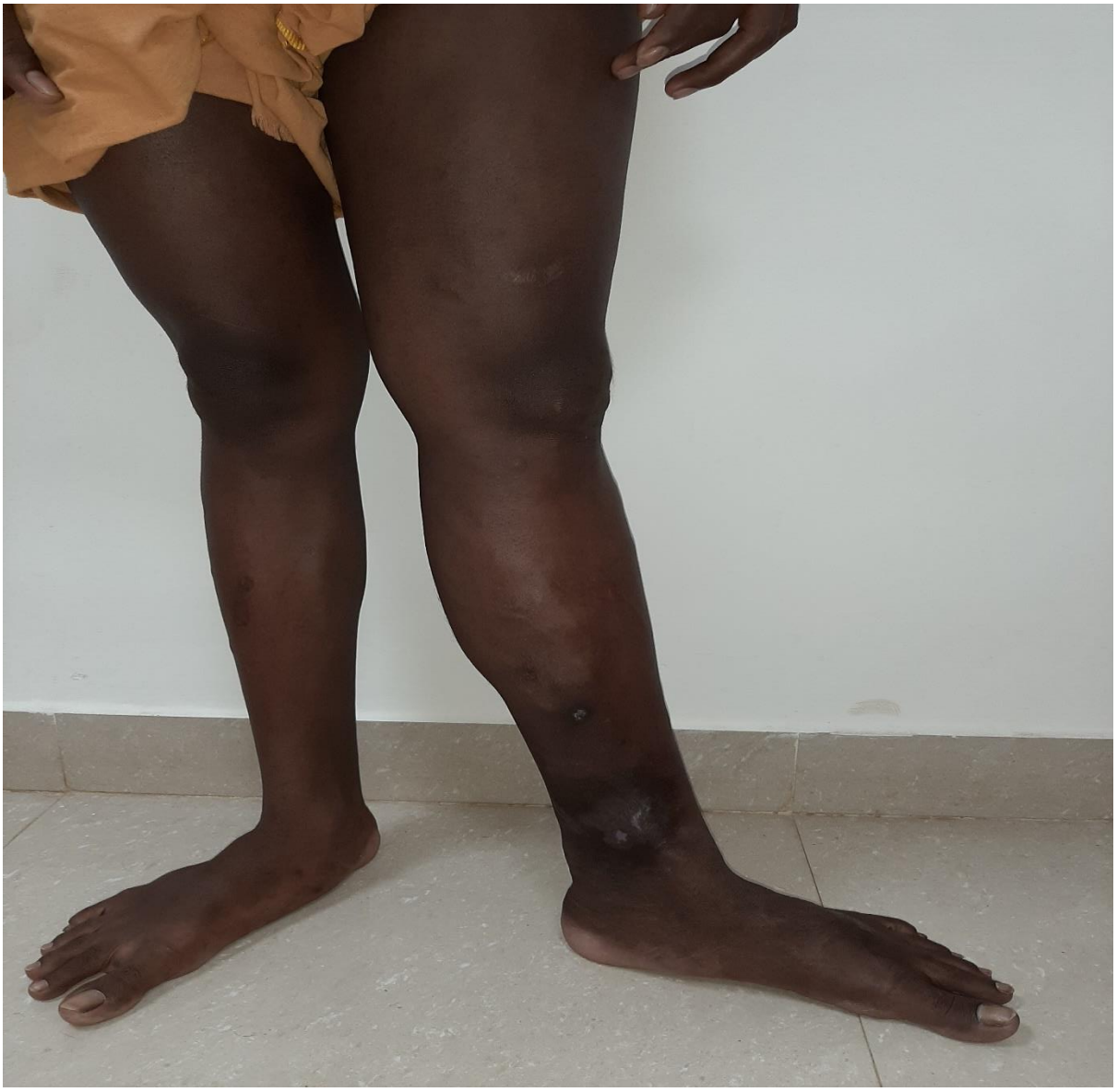
However, the Villalta scale also has limitations: venous claudication is not incorporated, and venous ulceration cannot be graded for severity. Post thrombotic syndrome is a chronic condition and therefore a diagnosis based on just one observation might not be ideal. Villalta scores tend to be unstable. This might lead to overestimation of the diagnosis, especially in patients with mild PTS. With little or no irreversible skin changes, total scores become more dependent on complaints.

Making a diagnosis on just one observation is therefore likely to result in a less precise estimation than making a diagnosis based on repeated scores. With a diagnosis based on just one assessment, patients will more often be diagnosed as having PTS; most of these patients will be classified as having mild PTS.

For the incidence of moderate and severe PTS it makes no difference, which definition of the Villalta score is used as the observed symptoms and signs are less likely to be reversible. For future clinical trials on PTS treatment it might be better to select patients with moderate to severe PTS based on the Villalta score and hence study the effect of a treatment in a less heterogeneous population to focus on those patients that are most likely to benefit.

LACK OF PREDICTION MODELS

Up till now there are no prediction models to identify patients at low or high risk for PTS. The fact that patients at risk cannot be identified at an early



point in time hampers timely and adequately directed therapy. One of the challenges for the construction of a prediction model for PTS is lack of an objective diagnosis.

The Villaltascore is a useful tool to diagnose PTS. The score is composed of 3 components; 5 symptoms, 6clinical signs and the presence or absence of venous ulceration. “A score <5 rules out PTS, a score of 5 to 9 diagnoses mild PTS, a score of 10 to 14 diagnoses moderate PTS while a score ≥15 or the presence of an ulcer diagnoses severe PTS”. In addition, ultrasound can be used toaid diagnosis and assess for lack of compressibility of the lower extremity deep veins or thepresence of venous reflux.

PTS effect on quality of life (QOL) PTS has a detrimental impact on the quality of life when compared with the general populationand also when compared to patients with DVT without PTS.

A Canadian study addressed the quality of life in PTS patients compared with patients with DVT who did not develop PTS.

Subjects with PTS has significantly worse disease-specific quality of life scores when compared to subjects without PTS, taking into consideration that 89% of the subjects in the PTS group had only mild to moderate disease.

In another prospective study in which 387 patients with DVT were followed for 2 years, 47% developed PTS and more than half of these had mild disease.

Over 2 years, the QOL tended to improve in patients with DVT except those patients who developed PTS; they reported significantly worse QOL scores comparable to patients withdiabetes, chronic obstructive pulmonary disease, congestive heart failure and even cancer.

Diagnosis refers to the act of establishing the nature of a problem, based on the presence of compatible clinical features. Through the process of diagnosis, we offer patients a label to identify their disease. The concept of severity refers to the degree of the disease, to the extent of organ involvement, and to the risk of an unwanted outcome.

There are no laboratory, imaging or functional tests to establish the diagnosis of PTS, which is solely defined by the presence of signs and symptomscombined with objectively confirmed DVT (i.e., by Doppler ultrasound, contrast venography, computerized tomographic venography, or magnetic resonance venography), irrespective of the presence of vein abnormalities detected by invasive or non-invasive tests.

As summarized by Henke and Comerota, “imaging is neither part of the definition of PTS, nor does it correlate with severity”. Physical findings are characteristic, and diagnosis is established by visual inspection of the limb.

Non-invasive diagnostic imaging such as plethysmography and Doppler ultrasound can reveal venous abnormalities, including valvular reflux, vein obstruction, and calf pump dysfunction. However, although documentation of reflux and obstruction may be a predictor of severe PTS in adult patients, these abnormalities may not present in patients with PTS, and may be encountered in patients without PTS.

In consequence, experts stress that PTS should not be diagnosed in the absence of clinical findings, regardless of the results of imaging studies.

INVESTIGATIONS: -

- D dimer
- Doppler
- Duplex
- MRI Venography
- Impedance Plethysmography
- Contrast Venography

D –DIMER:

Elevated D- dimer is not necessarily a risk factor causing VTE, but itshould be used and interpreted as a marker of hypercoagulability. D-dimer is formed when fibrin is proteolyzed by plasmin. The presenceof elevated levels of D-dimer in

the circulation signifies that endogenous fibrinolysis of a venous thrombus has yielded crosslinked fibrin.

The degree of D-dimer elevation with VTE may depend on the extent of disease, the duration of symptoms, and the use of anticoagulants, with lower D-dimer levels associated with less extensive disease, longer duration of symptoms, and anticoagulant use. Using D-dimer to preselect patients likely to have DVT has gained considerable interest in an effort to reduce costs and expedite patient work-up.

The D-dimer assays currently available are turbidimetry, ELISA, latex particle agglutination, fluorescence immunoassay and immunofiltration tests. Each assay has a corresponding normal reference range which is typically not interchangeable. There are situations where D-dimer assay may be falsely positive. These situations include pregnancy, malignancy, recent postoperative state and total bilirubin greater than 2mg/dl.

Further confounding factors may include the age of the clot as significant declines in the D-dimer level may occur with time, position of the clot and heparin use. Despite its limitations, D-dimer is a useful tool to rule out DVT as long as the threshold is set low enough to keep the sensitivity high.

DUPLEX:

Duplex ultrasound combines compression using realtime B-mode ultrasound with Doppler venous outflow detection.Its lack of radiation, portability, non-invasiveness and cost-effectiveness has made it superior to contrast venography. It also has the ability to distinguish non-vascular pathology such as inguinal adenopathy, Baker's cyst, abscesses and hematomas.

The sensitivity of compression sonography is high for proximal DVT and lower for non-occluding or isolated calf vein thrombosis. The pitfalls ofvenous duplex imaging include misidentification of veins,duplicated veinsystems, systemic illness or hypovolemia decreasing venous distension, suboptimal imaging in obese or oedematous patients, or areas not amenable to compression such as the iliac veins and adductor canal.

Normal venous flow assessment: -

Spontaneity – Spontaneous flow without augmentation

Phasicity – flow changes with respiration

Compression – Transverse plane

Augmentation – compression distal to site of examination, patency below site of examination

Valsalva –deep breath, strain, while holding the breath patency of abdominal and pelvic veins.

MAGNETIC RESONANCE VENOGRAPHY:

MRV has gained momentum in recent years for the detection of DVT. In addition to been less invasive than contrast venography MRV overcomes some of the limitation of Duplex and Impedance Plethysmography. Since MRV directly visualises the thrombus even non-flow limiting thrombi should be detectable unlike with impedance Plethysmography. MRV should also be able to detect thrombus proximal to the inguinal ligament, an area which has been problematic for duplex in the past. MRV results are also independent of the technologist's experience and availability. Its limitation includes high cost, patients with implants and renal insufficiency since gadolinium is associated with nephrogenic systemic fibrosis.

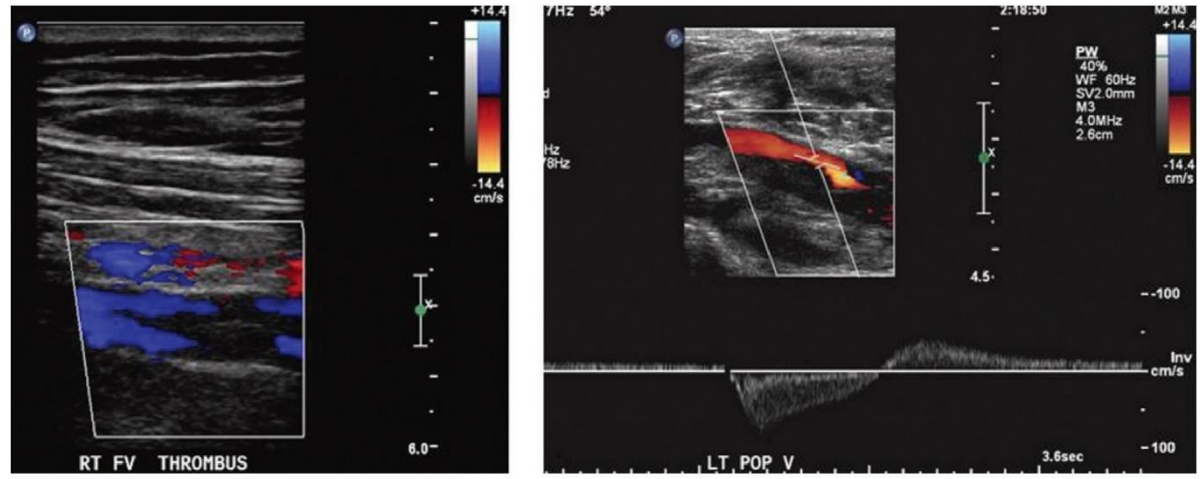
CONTRAST VENOGRAPHY:

Contrast venography has by default been long hailed as the gold standard for detection of symptomatic DVT. As of late, its current role in diagnosis of DVT has been largely relegated to one of historical interest. The study is limited in its practicality by both the availability of highly sensitive non-invasive studies and by its own disadvantages, including the risk of phlebitis, IV contrast load with associated risk of nephrotoxicity and allergic reaction, Increased cost and the need for adequate IV access. Available methods of performing venography, which have been emerged as dominant technique, as described by rabenow-paulin, involve spot films whereas the second technique involves long-leg films.

Rarely is CV a first line study, a role for CV is still exist when non-invasive studies are unavailable, non-diagnostic or in the presence of a clinical condition known to produce false results (e.g. –D dimer levels post operatively or during pregnancy, compression of the iliac veins in pregnant or recently postpartum women on an MRV study etc.

IMPEDENCE PLETHYSMOGRAPHY (IPG):

IPG is based upon the physiological principle that the impedance between 2 points on the skin of an extremity will decrease as the volume of blood contained in the extremity increases. The technique examines great at which venous outflow occurs, thereby deducing the presence or absence of venous outflow obstruction. The presence of DVT in the major vessels of the lower extremity including the popliteal vein and proximally, should reduce the rate of venous outflow and subsequently affect the tracing. In the instance of nonflow limiting thrombi, the study will be negative. Its limitation include inability to detect DVT distaltopopliteal vein.



A B

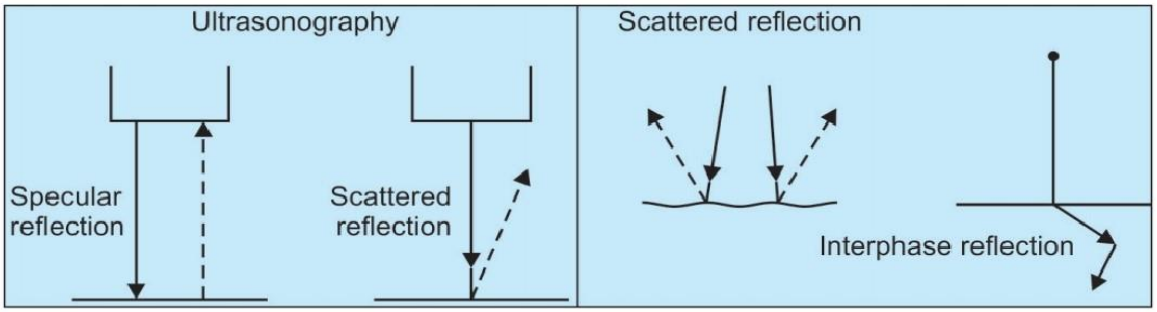
DUPLEX Images showing, A)thrombus in the right femoral vein, and B) thrombus in the left popliteal vein.

Several clinical indexes and instruments have been developed to evaluate PTS in adult patients. The Villalta Scale and the Clinical, Etiological, Anatomical and Pathophysiological classification (CEAP) are the most widely used instruments for evaluating LE PTS. The VS has been modified for the assessment of UE PTS in this population.

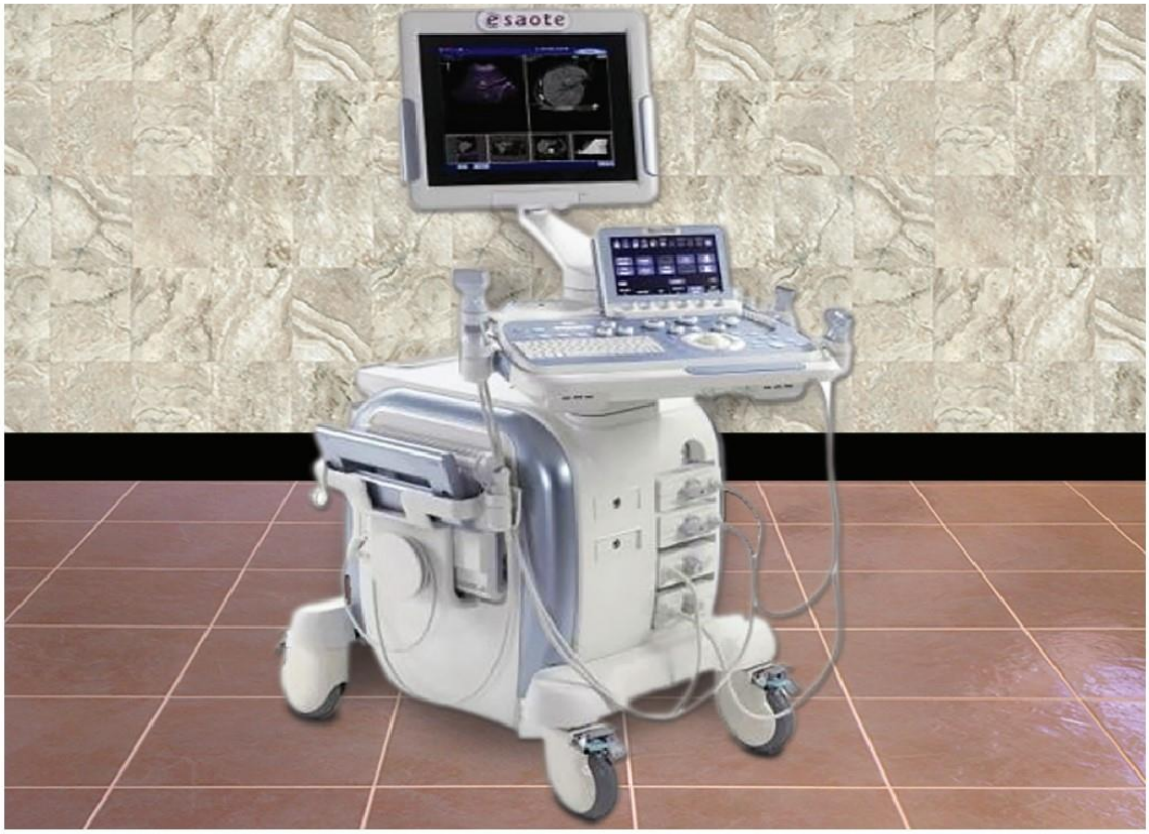
The ISTH recommends the VS as the standard instrument to diagnose and establish the severity of LE PTS in adults. The discriminative and evaluative purposes of the VS are supported by its measurement properties (reliability, validity, and responsiveness).

It assesses five subjective symptoms (heaviness, pain, cramps, pruritus, and paraesthesia), and seven objective signs (pretibial oedema, induration of the skin, hyperpigmentation, new venous ectasia, redness, pain during calf

compression, and ulceration of the skin). Each item, except for ulcers, is scored using a 0 to 3 scale (none to severe).



Principles of ultrasonography.



Ultrasonography machine.

The presence of ulcers is equivalent to a score of 15. A score ≥5 is diagnostic of PTS. A final score of 5-9 represents mild PTS, 10-14, moderate PTS, and >14, severe PTS.

Villalta PTS scale

Assessment of:	
• 5 symptoms (pain, cramps, heaviness, pruritus, paresthesia) by patient self-report	
• 6 signs (edema, skin induration, hyperpigmentation, venous ectasia, redness, pain during calf compression) by clinician assessment	
Severity of each symptom and sign is rated as 0 (absent), 1 (mild), 2 (moderate) or 3 (severe). In addition, ulcer is noted as present or absent.	
Points are summed to yield the total Villalta score:	
0-4:	No PTS
5-9:	Mild PTS
10-14:	Moderate PTS
≥15, or presence of ulcer	Severe PTS

CEAP is a descriptive classification system for venous diseases in general. It was developed to provide a basis for uniformity in reporting CVI, rather than a discriminative or evaluative PTS-specific instrument. Its basic form classifies patients according to clinical classes (seven classes), etiologic factors (four classes), anatomic distribution (four classes), and pathophysiological dysfunction (four classes). Clinical classes are as follows: C0 (No visible or palpable signs of venous disease), C1 (Telangiectasias or reticular veins), C2 (Varicose veins; distinguished from reticular veins by a diameter of 3 mm or more), C3 (Oedema), C4 (Changes in skin and subcutaneous tissue secondary to chronic venous disease, C4a pigmentation or eczema, C4b lipo- dermatosclerosis or atrophie blanche), C5 (Healed venous ulcer), C6 (Active venous ulcer). Each clinical class

can be recorded as symptomatic or asymptomatic, although symptoms are not specifically defined.

IMPORTANCE OF DIAGNOSIS AND SEVERITY RATING IN PTS

Once PTS is established, particularly if complicated by skin ulcers, it can lead to significant disability and poor HRQoL in adult patients, even poorer than that of patients with other forms of CVI. It has been reported that patients with severe PTS have worse generic physical HRQoL than patients with chronic lung disease, osteoarthritis, and angina.

In addition, PTS sustains a particularly high direct medical cost as well as an indirect cost driven by loss of productivity. In 1997, a Swedish study estimated that the average cost of treating DVT complications was 75% of the estimated cost of treating the index DVT. The total health care cost has been estimated to be 32%-50% higher in patients with PTS than in patients with DVT who do not develop PTS. Leg ulcers have been associated with time lost from work and job loss, particularly in young adults.

The negative repercussion of PTS is largely due to the limited options to treat this syndrome. PTS treatment is challenging and frustrating as it can only target the improvement of symptoms, rather than restoring the normal physiology of the venous system.

In fact, there is no effective treatment for PTS to date. For this reason, PTS prevention is considered paramount and is the focus of research efforts, especially among adult patients.

Until recently, graduated elastic compression garments were indicated for the prevention of PTS in adults at risk of developing this complication (i.e., patients who sustained DVT). Supporting their use, a pooled analysis of randomized controlled trials (RCT) conducted between the 1990s and the early 2000s, which included a total of 628 patients (320 assigned to the intervention group, 308 to the control group), concluded that compression garments reduced the incidence of PTS by 50%. Even though the studies differed at several levels (type and pressure of the garment, time to starting the intervention, length of follow up, blinding, and comparator group – placebo vs. no intervention), they all showed a lower absolute frequency of PTS in patients assigned to the compression garment arm. For more than 10 years these studies provided the rationale for the recommendation of prescribing compression garments to prevent PTS as an evidence-based therapeutic option.

However, the efficacy of garments for PTS prevention in adults at risk has since been challenged. The SOX trial, a more recent and larger RCT that enrolled 806 patients (410 assigned to the intervention and 396 to placebo garments), showed compression garments to have no effect. Although poor patient compliance has surfaced as one of the potential underlying factors that could explain these conflicting results, the findings of the SOX trial shifted the opinion of experts, as reflected in the change in the recommendations regarding the indication of compression garments with preventive purposes.

The role of thrombolysis for the prevention of PTS in children is unclear. Published experience consists of a few small case-series and cohort studies that investigated the safety and efficacy in terms of short-term outcomes (thrombosis resolution).

Thrombus resolution was found to be a predictor of PTS in our patients, which is not surprising, given the link between thrombus resolution and inflammation and the bearing of both on the pathophysiology of PTS. This finding suggests that, if thrombolysis leads to complete resolution of VTE, it could prevent PTS.

However, there are also some risks associated with thrombolysis.

To successfully conduct further research in this area, better tools for the diagnosis and evaluation of severity are required.

The careful selection of the items that should be included in a tool, the development of operational definitions of the items as well as of an adequate scoring system for the items are essential to the construction an instrument.

Aggressive treatment of the index thrombosis using catheter directed or pharmaco-mechanical thrombolysis is now being intensively investigated in adult patients, and it appears to have a role in the prevention of PTS in selected cases in this population.

The results of the Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial and the CAtheter Versus Anticoagulation Alone for Acute Primary (Ilio)Femoral DVT (DUTCH CAVA) trial are anticipated to address this pressing issue.

However, to successfully conduct further research in this area, better tools for the diagnosis and evaluation of severity are required.

ECONOMIC BURDEN

PTS not only affects QOL but also leads to considerable financial burden. The total annual treatment cost is 30% higher in patients who experience PTS after VTE compared to patients without PTS.

PREVENTION

Anticoagulation therapy plays an essential role in PTS prevention by preventing recurrence or propagation of DVT. However, sub-therapeutic anticoagulation is an independent risk factor for PTS development. Therefore, the most recent Chest Guidelines for antithrombotic therapy for VTE recommends a novel oral anticoagulant (NOAC) over a Vitamin K antagonist (Grade 2b).

Cheung YW et al48 studied the incidence of PTS in subjects who were treated with Rivaroxaban versus Enoxaparin/ Coumadin. “The cumulative PTS

incidence at 60 months follow-up was 29 % in the Rivaroxaban group and 40 % in the enoxaparin/ vitamin K antagonist (VKA) group"; However, this did not reach statistical significance with a hazard ratio of 0.76 (95 % CI: 0.511.13). The effect of other NOACs on the development of PTS has not yet been studied.

Theoretically low molecular weight heparins (LMWHs) could have a more favourable effect on preventing PTS because of their anti-inflammatory properties. In a study by González-Fajardo et al 165 patients with symptomatic, unilateral, first-episode DVT were randomized to treatment with coumadin or enoxaparin for at least 3 months, and then the 2 groups were followed for 5 years. Results revealed a lower recurrence rate of DVT in the enoxaparin group (19.3% vs 36.6% p = 0.02) and a decreased incidence of severe PTS (19.6% vs 29.5%); the latter not reaching statistical significance.

Given the underlying inflammatory process involved in the development of PTS, the anti-inflammatory properties of statins have been postulated to be beneficial. A randomized trial tested the effect of rosuvastatin on patients with DVT. The rosuvastatin arm had a significantly lower incidence of PTS development (38.3 % vs. 48.5%, p = 0.019).

ELASTIC COMPRESSION STOCKINGS

Early studies that addressed the role of elastic compression stockings (ECS) on PTS prevention showed a reduced incidence of PTS. Since the majority of these studies were not blinded, observational bias cannot be excluded. Moreover, the only multicentre, double blinded, randomized placebo-control trial (SOX) did not show a statistically significant difference in the incidence of PTS between those randomized to compression stockings versus those randomizedto placebo (hazard ratio, 1.13; 95% CI, 0.73–1.76).

Two meta-analyses also suggested benefit to ECS in the prevention of PTS. Nevertheless, it may be reasonable to prescribe compression stockings to reduce symptomatic swelling according to the AHA guidelines recommendation (Class IIb; Level of Evidence A).

The mainstay of medical therapy has been anticoagulation since the introduction of heparin in the 1930s.Other anticoagulation drugs have subsequently been added to the treatment armamentarium over the years, such as vitamin K antagonists and low-molecular-weight heparin (LMWH). Anticoagulant therapy is recommended for 3-12 months depending on site of thrombosis and on the ongoing presence of risk factors. If DVT recurs, if a chronic hypercoagulability is identified, or if PE is life threatening, lifetime anticoagulation therapy may be recommended. This treatment protocol has a cumulative risk of bleeding complications of less than 12%.

THROMBOLYTIC THERAPY

Early and more complete thrombus clearance can relieve venous outflow obstruction, preserve valvular function, and reduce venous hypertension. The 'open vein' hypothesis has been supported by a meta-analysis including 17 RCTs (1103 participants) that included different methods of thrombolysis (CDT, local (through peripheral vein), systemic).

This showed significantly lower incidence of PTS in those receiving thrombolysis (RR 0.66, 95% CI 0.53 to 0.81; P < 0.0001) for up to 5 years of follow up after the DVT. However, this was at the expense of increased major bleeding (RR 2.23; 95% CI 1.41 to 3.52, P = 0.0006).

Systemic thrombolysis showed promising significant reduction in residual thrombosis and PTS development however it increased risk of major bleeding by 3-fold compared with conventional anticoagulation therapy58,59. Consequently, AHA guidelines recommended against use of systemic thrombolysis in acute DVT Class III; Level of Evidence A).

CONTRAINDICATION OF ANTICOAGULATION: -

- Absolute contraindications include
- Intracranial bleeding
- Severe active bleeding
- Recent brain, eye, or spinal cord surgery
- Pregnancy

- Malignant hypertension.
- Relative contraindications include
- Recent major surgery
- Recent cerebrovascular accident
- Severe thrombocytopenia

HEPARIN THERAPY: -

Heparin is a heterogeneous mixture of polysaccharide fragments with varying molecular weights but with similar biological activity. The larger fragments exert their anticoagulant effect by interacting with antithrombin III (ATIII) to inhibit thrombin. ATIII, the body's primary anticoagulant, inactivates thrombin and inhibits the activity of activated factor X in the coagulation process. Heparin prevents extension of the thrombus and has been shown to significantly reduce (but not eliminate) the incidence of fatal and nonfatal pulmonary embolism and recurrent thrombosis.

Heparin Protocol: -

Administer initial intravenous heparin bolus 5000U

- Administer continuous intravenous heparin infusion: commence at 42 ml/h of

- 20000U (1680U/h) in 500 ml of two-thirds dextrose and one-third saline (a 24
- hour heparin dose of 40320U), except in following patients in whom heparin infusion is commenced at a rate of 31 mL/h (1240U/h, a 24-hour dose of 29760U)
- Patient who have undergone surgery within the previous 2 weeks
- Patients with a previous history of peptic ulcer disease or gastrointestinalandgenitourinary bleeding.
- Patient with recent stroke (thrombotic stroke within 2 weeks previously)
- Patients with a platelet count <150 x 10*9/L
- Patients with miscellaneous reasons for a high risk of bleeding (e.g.: - hepatic failure, renal failure, or Vitamin K deficiency)
- Adjust heparin dose by use of aPTT. The aPTT test is performed in all patients as follows,
- 4-6 hours after commencing heparin, the heparin dose is then adjusted
- 4-6 hours after the first dose adjustment, then as indicated by the nomogram for the first 24 hours of therapy.

Thereafter once daily, unless the patient is sub therapeutic (< 1.5 times the mean normal control value for the thromboplastin reagent being used) in which case the aPTT test is repeated 4-6 hours after the heparin dose is increased.

Although there is a strong correlation between sub therapeutic aPTT values and recurrent Thromboembolism, the relationship between sub therapeutic aPTT and bleeding is less definite. Indeed, bleeding during heparin therapy is more closely related to underlying clinical risk factors than to aPTT elevation above the therapeutic range. Studies confirm that weight and age > 65 are independent risk factors for bleeding on heparin.

Complications of Heparin therapy: -

- Bleeding
- Thrombocytopenia
- Osteoporosis
- Heparin induced thrombocytopenia

Low Molecular weight Heparin: -

Low-molecular-weight heparins (LMWHs) are a new class of anticoagulants derived from unfractionated heparin (UFH). They have a number of advantages over UFH that have led to their increasing use for a number of thromboembolic indications.

They differ from UFH in many ways, of particular importance are the following: -

- Increased bioavailability

- Prolonged half life
- Predictable clearance enabling once or twice daily injection, and predictable
- antithrombotic effect based on body weight permitting treatment without
- laboratory monitoring.
- Ability to inactivate platelet bound factor Xa, resistance to inhibition by

platelet factor IV, and their decreased effect on platelet function and vascular permeability, possibly accounting for less haemorrhagic effects at comparable antithrombotic doses. Though there are complications like bleeding, Heparin induced thrombocytopenia, osteoporosis, with LMWH the incidence is much lower when compared to UFH.

If heparin induce thrombocytopenia occurs LMWH should be stopped and an alternative such as argatraban or hirudin derivative should be commenced.

ORAL VITAMIN K ANTAGONIST: -

There are 2 distinct chemical groups of oral anticoagulants

4-hydroxy coumarin derivatives (e.g.; warfarin)

Indanedione derivatives (e.g.; Phenindione)

The coumarin derivatives are the anticoagulants of choice because they are associated with fewer non-haemorrhagic adverse effects than the Indanedione derivatives.

Anticoagulation effect of warfarin id mediated by the inhibition of Vitamin K dependant coagulation factors, II,VII,IXand X.

The anticoagulant effect of warfarin is delayed until the normal clotting factors are cleared from circulation, and the peak effect does not occur until 36-72 hours after drug administration. Heparin and warfarin treatment should overlap by 4-5 days.

The lab test most commonly used to measure the effects of warfarin is the one stage PT test. To promote standardization of the PT monitoring, WHO (World Health organization) enveloped an international reference thromboplastin from human brain tissue and recommended at the PT ratio to be expressed as the International normalized ratio, or INR. The monitoring and dosing of the oral anticoagulant therapy is done according to the INR value.

Warfarin is administered in an initial small dose for the first 2 days, then the dose adjusted according to the INR value. Heparin therapy is discontinued in the 4th or 5th day following initiation of warfarin therapy, provided the INR is in the therapeutic range (INR 2-3).

The dose response relationship of warfarin therapy varies widely between individuals and therefor the dose must be carefully monitored to prevent under dosing or over dosing. Patient should be warned against taking any new drugs without the knowledge of their attending physician in view of drug interaction. Once the anticoagulant effect and patient's warfarin dose requirements are stable, the INR should be monitored at regular intervals throughout the course of warfarin therapy for VTE for maintenance of the narrow therapeutic range.

COMPLICATIONS OF WARFARIN

- Major adverse effects are bleeding
- Coumarin induced skin necrosis – it is a serious complication, most commonly seen in women. It occurs between 3 to 10 days after therapy has commenced. Most common locations are areas with abundant subcutaneous tissue such as the abdomen, buttocks, thighs and the breast.

The antidote used for vitamin K antagonists is Vitamin K1.

FACTOR XA AND DIRECT THROMBIN INHIBITORS: -

Fondaparinux

Fondaparinux, a direct selective inhibitor of factor Xa, overcomes many of the aforementioned disadvantages of low-molecular-weight heparins (LMWHs). Pharmacokinetic studies of fondaparinux reveal that only a single-daily subcutaneous dose is required. Furthermore, a single dose of 7.5mg is effective over a wide range of patient weights between 50 and 100 kg. Daily doses of 5 mg or 10 mg are appropriate for patients who weigh less or more than that weight range.

Heparin-induced thrombocytopenia (HIT) has not been reported. Therapeutic monitoring of laboratory parameters such as the prothrombin time or activated partial thromboplastin time (aPTT) is also not required.

In some regions, the cost of therapy with fondaparinux is less than enoxaparin when it is being used to bridge therapy to a vitamin K antagonist (VKA).

The combination of two factors X a inhibitor may be an effective treatment strategy for acute venous thromboembolism (VTE).

Rivaroxaban

Rivaroxaban (Xarelto) is an oral factor X a inhibitor approved by the FDA in November 2012 for treatment of DVT or pulmonary embolism (PE) and for reduction of the risk of recurrent DVT and PE after initial treatment.

Approval for this indication was based on studies totalling 9478 patients with DVT or PE. Participants were randomly assigned to receive Rivaroxaban, a combination of enoxaparin and a VKA (e.g., warfarin), or a placebo. Study endpoints were designed to measure the number of patients who experienced recurrent symptoms of DVT, PE, or death after receiving treatment. Data from a pooled analysis of the EINSTEIN-DVT and EINSTEIN-PE trials suggested that Rivaroxaban is as effective in preventing VTE recurrence as enoxaparin followed by a VKA and may be associated with less bleeding in addition, the data suggested that there are no grounds for avoiding Rivaroxaban use in high-risk groups 26(e.g., fragile patients, cancer patients, and patients with a large clot).

Approximately 2.1% of patients treated with rivaroxaban experienced recurrent DVT or PE, compared with 1.8-3% treated with the enoxaparin and VKA combination.

Additionally, results from extended treatment demonstrated a reduced risk of recurrent DVT and PE. Approximately 1.3% in the rivaroxaban group experienced recurrent DVT or PE, compared with 7.1% in the placebo group.

Apixaban

In March 2014, the FDA approved apixaban (Eliquis) for the additional indication of prophylaxis of DVT and PE in adults who have undergone hip- or knee-replacement surgery.

Support for this new indication was a result of the ADVANCE 1, 2, and 3 clinical trials that enrolled nearly 12,000 patients.

Apixaban was originally approved by the FDA in December 2012 for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

In August 2014, apixaban was approved for treatment of DVT and PE. The approval for treatment of PE and prevention of recurrence was based on the outcome of the AMPLIFY (Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy) and AMPLIFY EXT (extended treatment) studies, in which apixaban therapy was compared with enoxaparin and warfarin treatment.

The AMPLIFY study showed that, in comparison with the standard anticoagulant regimen, apixaban therapy resulted in a 16% reduction in the risk of a composite endpoint that included recurrent symptomatic venous thromboembolism (VTE) or VTE-associated death.

Data from the AMPLIFY-EXT trial showed that extended anticoagulation (12 months) with apixaban shortened hospital stays, reduced symptomatic recurrent venous thromboembolism or all-cause death without an associated increase in major episodes of haemorrhage when compared with placebo.

Dabigatran

Dabigatran (Pradaxa) inhibits free and clot-bound thrombin and thrombin induced platelet aggregation. This agent was FDA approved in 2010 to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. In April 2014, it was approved for the treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for 5-10 days. Additionally, it was approved to reduce the risk of DVT and PE recurrence in patients who have been previously treated.

Approval was based on results from 4 global phase III trials that showed Dabigatran was non-inferior to warfarin and had a lower risk of major or clinically relevant bleedingcompared with warfarin. There have been reports of severe and fatal bleeding in users of the drug.

The RE-COVER and RE-COVER II trials included patients with DVT and PE who were treated with parenteral anticoagulant therapy for 5-10 days. Results showed Dabigatran was non-inferior to warfarin in reducing DVT and PE after a median of 174 days of treatment with a lower risk of bleeding compared with warfarin.

The RE-SONATE trial and RE-MEDY trials included patients (n=2856) with acute DVT and PE who had completed at least 3 months of anticoagulant

therapy. Results from this trial showed Dabigatran was non-inferior to warfarin in the extended treatment of VTE and carried a lower risk of major or clinically relevant bleeding than warfarin.

Edoxaban

Edoxaban was approved by the FDA in January 2015 for the treatment of DVT and PE in patients who have been initially treated with a parenteral anticoagulant for 5-10 days. Approval was based on the Hokusai VTE study that included 4,921 patients with DVT and 3,319 patients with PE. Among patients with PE, 938 had right ventricular dysfunction, as assessed by measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. There was a 3.3% rate of recurrent VTE in this subgroup in those who received Edoxaban compared to 6.2% in the group that received warfarin. The investigators concluded that Edoxaban was not only non-inferior to high-quality standard warfarin therapy but also caused significantly less bleeding in a broad spectrum of patients with VTE, including those with severe PE.

Reversal of Anticoagulation

Anticoagulation-related major bleeding is associated with an increased risk of death and thrombotic events, independent of the class of anticoagulant used. Although older agents of anticoagulation and their reversal are well studied, the newer agents lack similar antidotes. With the increasing use of non–vitamin K antagonist oral anticoagulants (NOAC), the number of patients who require reversal of their anticoagulant effects can be expected to rise.

The following section describes the reversal agents for both older and new anticoagulants.

Heparin

Heparin has a relatively short half-life of about 60–90 minutes and, therefore, the anticoagulant effect of therapeutic doses of heparin will mostly be eliminated at 3-4 hours after termination of continuous intravenous administration. For a more immediate neutralization of heparin, protamine sulfate can be administered at a dose of 1 mg for every 100 units of heparin.

Lower molecular weight heparins

Currently, there are no specific antidotes to low molecular weight heparins. Recombinant FVII a (rVII A) has been shown to stop bleeding in patients anticoagulated with fondaparinux; however, no randomized controlled trials on such patients have been conducted.

Vitamin K

In patients with clinically significant bleeding, vitamin K can be used to reverse the anticoagulant effect of vitamin K antagonists (VKA). Vitamin K can be given orally or intravenously. The parenteral route has a more rapid onset; however, it is associated with a slightly increased risk of allergic reaction.

Fresh frozen plasma (FFP)

In case of a life-threatening emergency, FFP can be used for the reversal of VKA. FFP contains all the coagulation factors in normal concentrations. However, FFP should be used with caution, as it has the potential to cause volume overload, allergic reaction, and transfusion-related reactions.

Prothrombin complex concentrates (PCCs)

In the case of serious and life-threatening bleeding, immediate correction of the international normalized ratio (INR) can be achieved by the administration of PCCs. These contain 3 or 4 of the vitamin K–dependent coagulation factors, as well as proteins C and S. In a prospective study, administration of PCCs has been shown to result in sustained haemostasis in patients using VKA. Non–vitamin K antagonist oral anticoagulants (NOACs) The new oral anticoagulant factor X a or II a inhibitor have numerous advantages over traditional VKAs, including rapid therapeutic effectiveness, ease of dosing, and lack of monitoring. Until recently, there were no approved drug-specific reversal agents for the NOACs.

A number of drugs are currently under development. Due to the short half-life of F X a inhibitors, discontinuation of the drugs suffice in clinical situations in which there is time to await spontaneous clearance.

Currently, PCCs can be used to address severe bleeding in patients taking NOACs when administered in high enough dosages. Some guidelines suggest an initial dose of 25 to 50 U/kg of PCCs in life-threatening emergencies, to be repeated if necessary.

Idarucizumab

Idarucizumab is a humanized antibody fragment directed against Dabigatran. This agent has been shown to completely reverse the anticoagulant effect of Dabigatran within minutes; on October 16, 2015, it was approved by the FDA as an antidote for Dabigatran.

Andexanet alfa

Andexanet alfa is a recombinant, modified F X a molecule that acts as a decoy protein that is catalytically inactive but has a high affinity for F X a inhibitors. It is being developed as an antidote for apixaban, Edoxaban, and Rivaroxaban. Andexanet alfa has been shown to reverse the anticoagulant effects of apixaban and Rivaroxaban in human volunteers, and more studies are ongoing.

Aripazine

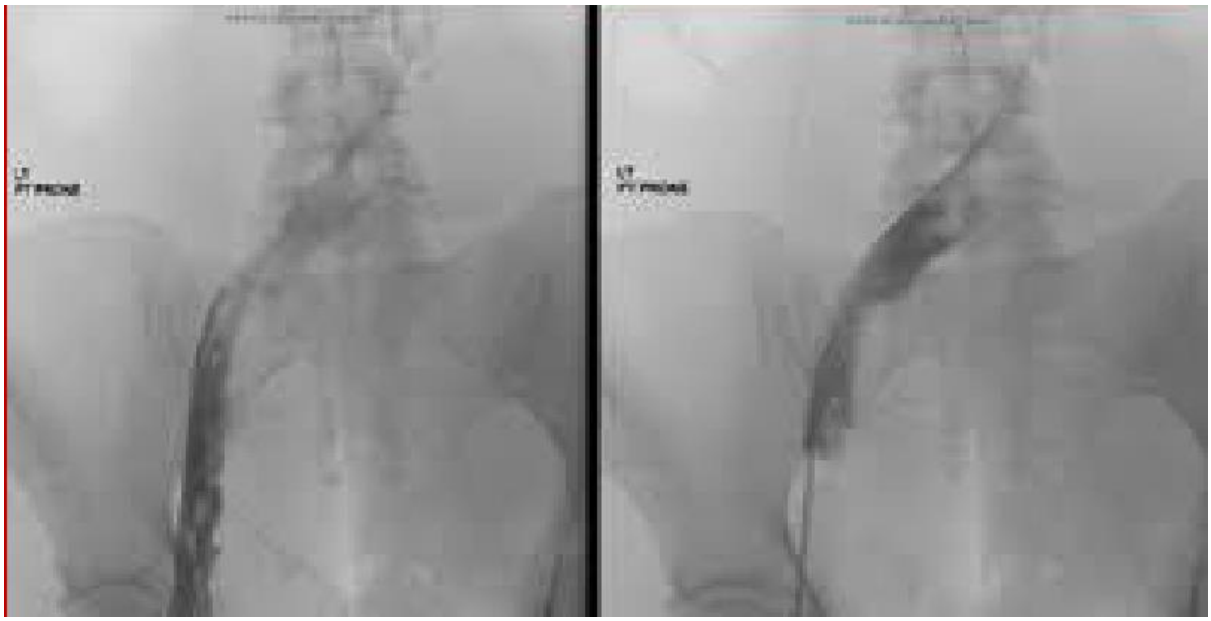
Aripazine is a synthetic small molecule that has broad activity against both old (Heparin, low molecular weight heparin) and new oral anticoagulants (Dabigatran, Rivaroxaban, apixaban, Edoxaban). A 2014 study of human volunteers demonstrated that administration of Aripazine reversed the prolonged clotting time caused by Edoxaban.

CATHETER DIRECTED THERAPY

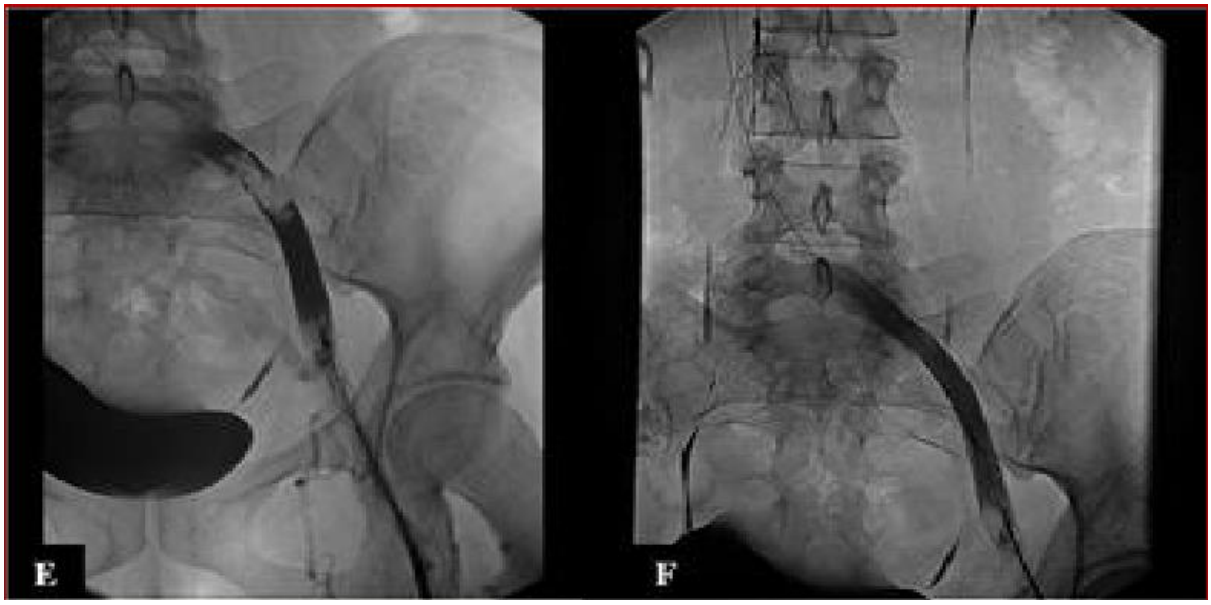
Catheter directed therapy (CDT) seemed to be an alternative option for decreasing the incidence of PTS with reduction of bleeding events compared to systemic lytic therapy. The CaVen-T study was an open label randomized study in which patients with Ilio-femoral DVT were assigned to CDT and VKA therapy versus VKA therapy. The absolute risk reduction with CDT therapy was 14% after 2 years and increased to 28% after 5 years and the number needed to treat decreased from seven to four. No bleeding incidents were reported in both groups between 2 and 5 year follow up.

Similarly, in the TORPEDO trial, 183 patients with proximal DVT were randomized to percutaneous endovascular intervention (PEVI) plus anticoagulation therapy versus anticoagulation therapy alone. The patients were followed up for 30 months for incidence of PTS, DVT and PE. 6 out of 91 patients developed PTS in PEVI group versus 24 out of 92 in the control arm (3.4% vs 27.7% P = <0.001).

Therefore, PEVI with anticoagulation reduced the incidence of PTS; however, the ATTRACT trial failed to demonstrate any significant difference in the incidence of PTS between the intervention group and conventional anticoagulation therapy group within 2 years of follow up (46.7% versus 48.2% P=0.56) and also showed patients in the intervention arm to have a significantly higher minor and major bleeding events.



Although the results showed no significant outcomes between the 2 groups, the authors concluded that pharmaco-mechanical CDT reduces early deep vein thrombosis symptoms and post-thrombotic syndrome severity. In addition, a subgroup analysis showed that CDT may be of benefit to patients with symptomatic acute ilio-femoral DVT.



The most recent VTE treatment guideline advocates anticoagulation alone over CDT therapy; however, it left the decision to choose an interventional option up to the patient and the physician after taking into account patient preference, the perceived importance of post-thrombotic syndrome, the risk of bleeding and cost.

MATERIALS AND METHODS

This study was conducted in Thanjavur medical college & hospital between the period of October 2017 - September 2019.

The study includes patients presenting with complaints of lower limb pain, heaviness, altered sensation, skin discoloration, swelling admitted in surgical wards during the above-mentioned period.

Detailed history was taken and a thorough physical examination was done. All details were recorded in the above mentioned proforma.

The recorded details include patient's particulars, symptoms & signs of PTS. All patients were subjected to USG Doppler / MRV / D- dimer and involved segments noted.

INCLUSION CRITERA

1. All patients with clinical diagnosis of post phlebitis lower limb.

EXCLUSION CRITERIA

1. Post phlebitis syndrome involving upper limb.

2. Primary varicose veins.

STUDY DESIGN

This is a prospective study conducted in our institution, Thanjavur Medical College during the period October 2017- September 2018. Patients were subjected for detailed history and clinical examination. and then investigated with Doppler/Duplex ultrasound. All patients were treated with IV anticoagulants and improved. Later changed to oral anticoagulants. Patients were discharged and advised to continue oral anticoagulants.

OBSERVATIONS &RESULTS:-

STATISTICAL ANALYSIS

Data were entered in the excel spread sheet and variables were coded accordingly. The statistical analyses were performed using Graph pad Prism version 5 software. Data were presented as mean with Standard deviation for normal distribution/scale data. Data were presented as frequency with proportion n (%) for categorical data. Fisher's exact test was used to compare the frequencies between the groups. One-Way ANOVA with Tukey's post hoc test was used to compare the variances between the four groups. $p<0.05$ were considered statistically significant.

Table 1. Frequency distribution of duration of age category observed in the study.

Sl.No	Age category	n	%
1	20 – 40 years	12	48

2	41 – 60 years	11	44
3	>60 years	2	8

Data are expressed as n with %. The total N=25. The mean age in the study was 31.7 years with SD of 11.3 years. The minimum age observed was 23 and the maximum was 70 years.

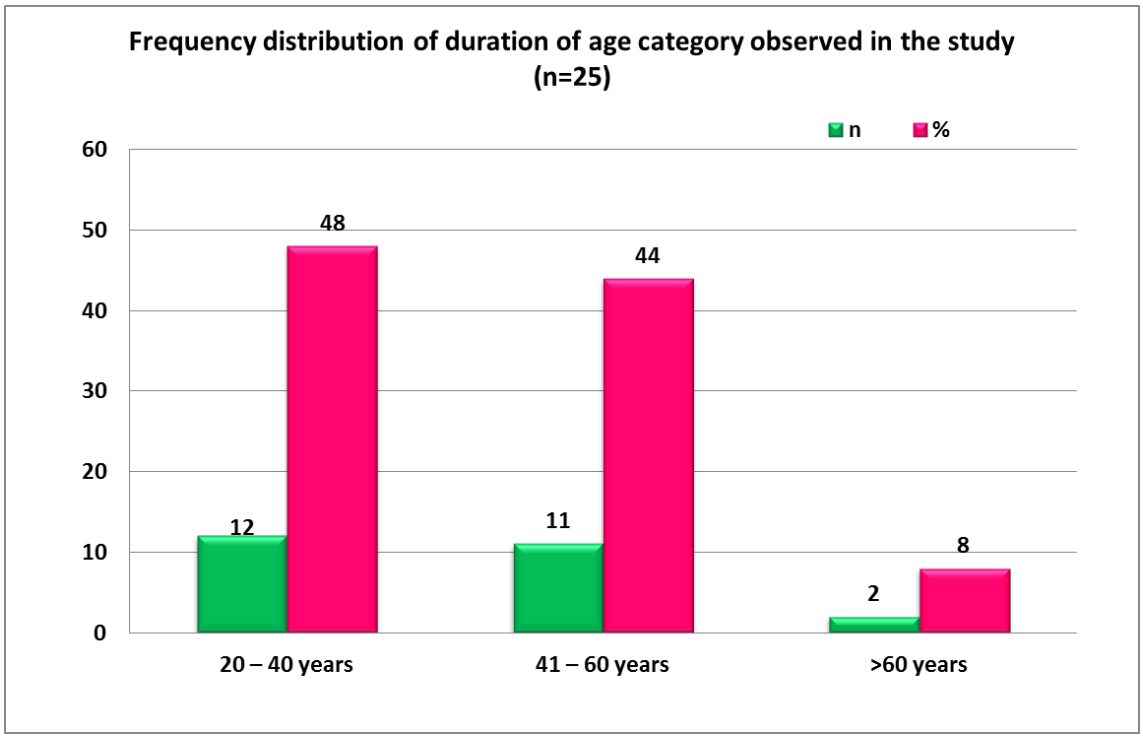


Table 2. Frequency distribution of gender category observed in the study.

Sl.No	Gender	n	%
1	Female	5	20
2	Male	20	80

Data are expressed as n with %. The total N=25.

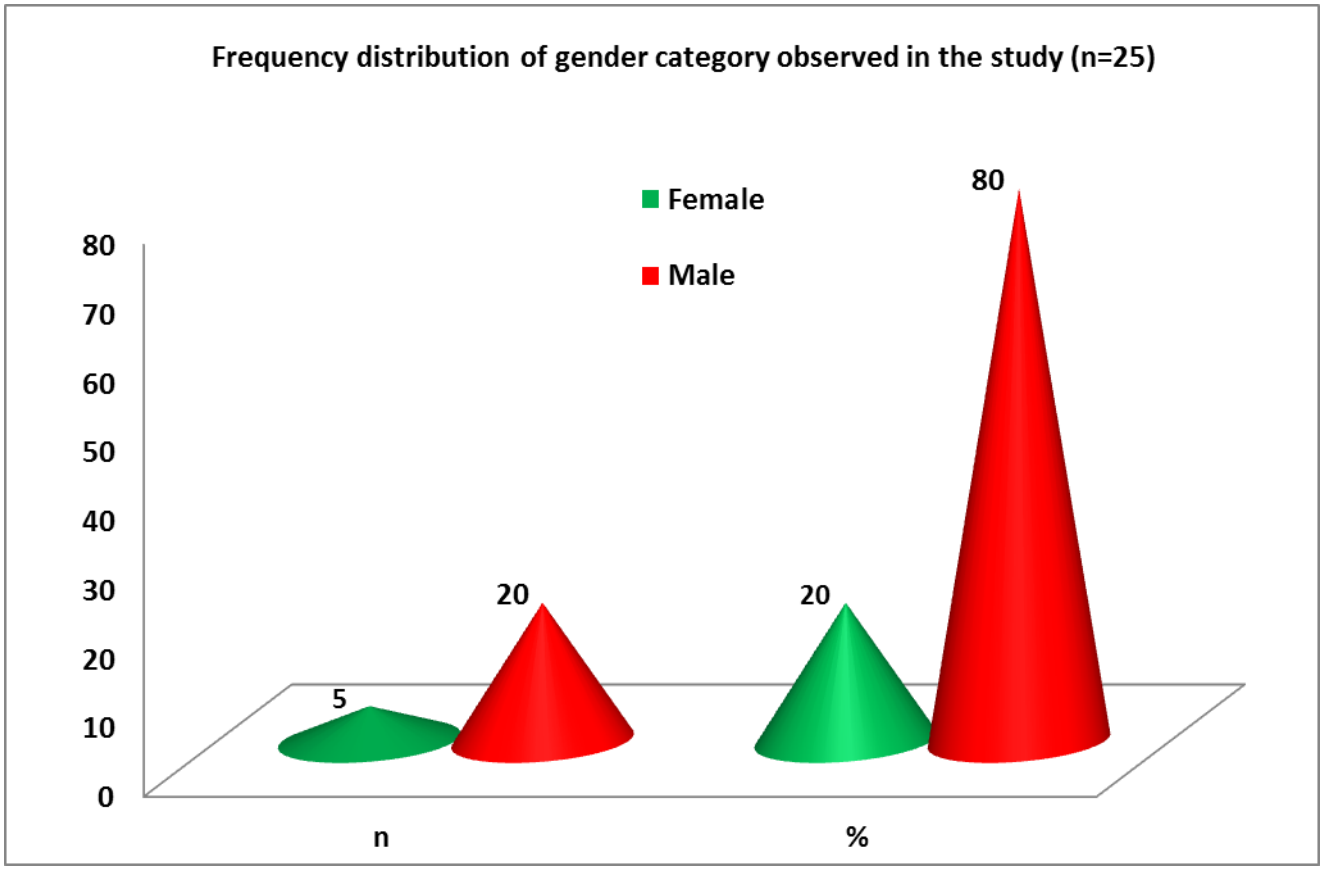
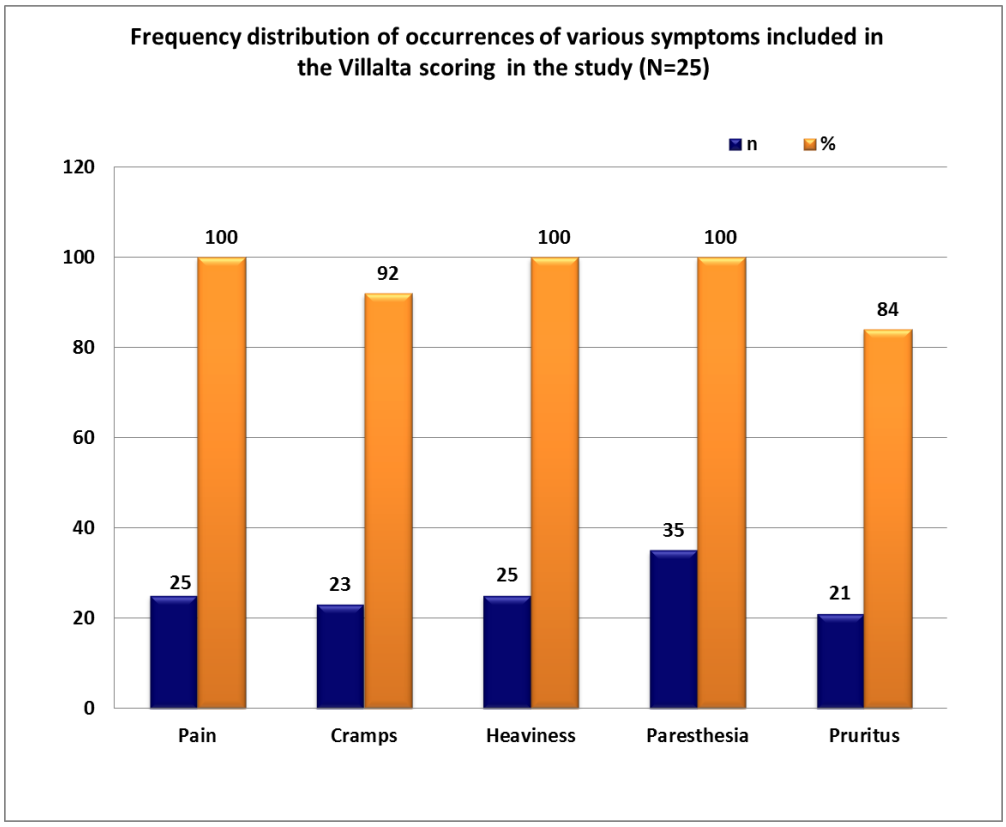


Table 3. Frequency distribution of occurrences of various symptoms included in the Villalta scoring in the study.

Sl.No	Type of symptoms	n	%
1	**PAIN**		
	Mild	13	52
	Moderate	11	44
	severe	1	4
2	**CRAMPS**		
	Absent	2	8
	Mild	17	68
	Moderate	5	20
	Severe	1	4
3	**HEAVINESS**		
	Mild	10	40
	Moderate	14	56
	Severe	1	4
4	**PARESTHESIA**		
	Mild	18	72
	Moderate	7	28
5	**PRURITUS**		

	Absent	4	16
	Mild	14	56
	Moderate	6	24
	Severe	1	4



Data are expressed as n with %. The total N=25.

Table 4. Frequency distribution of occurrences of various signs included in the Villalta scoring in the study.

Sl.No	Type of signs	n	%
1	**Pretibial edema**		
	Absent	1	4
	Mild	20	80
	Moderate	4	16
2	**Skin induration**		
	Mild	9	36
	Moderate	16	64
3	**Hyperpigmentation**		
	Moderate	17	68
	Severe	8	32
4	**Redness**		
	Absent	11	44
	Mild	13	52
	Moderate	1	4
5	**Venous ectasia**		
	Mild	14	56
	Moderate	11	44

6	**Tenderness on calf compression**		
	Absent	18	72
	Mild	3	12
	Moderate	4	16

Data are expressed as n with %. The total N=25.

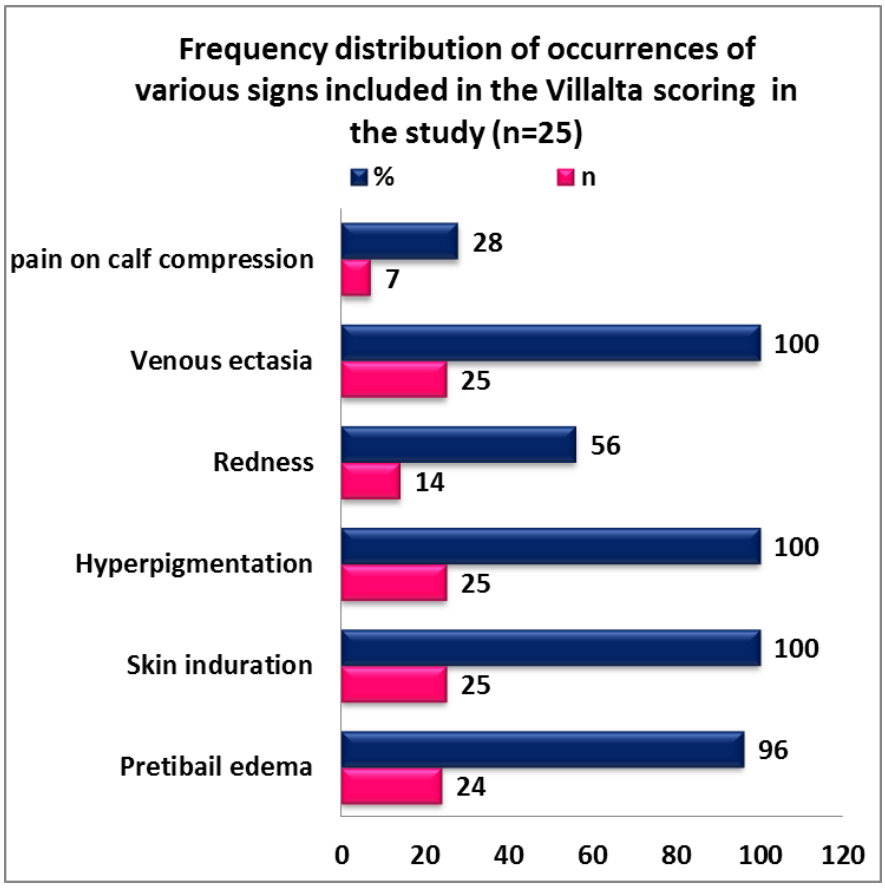


Table 5. Frequency distribution of occurrence of venous ulcer in the study.

Sl.No	Venous ulcer	n	%
1	Absent	10	40
2	Present	15	60

Data are expressed as n with %. The total N=25.

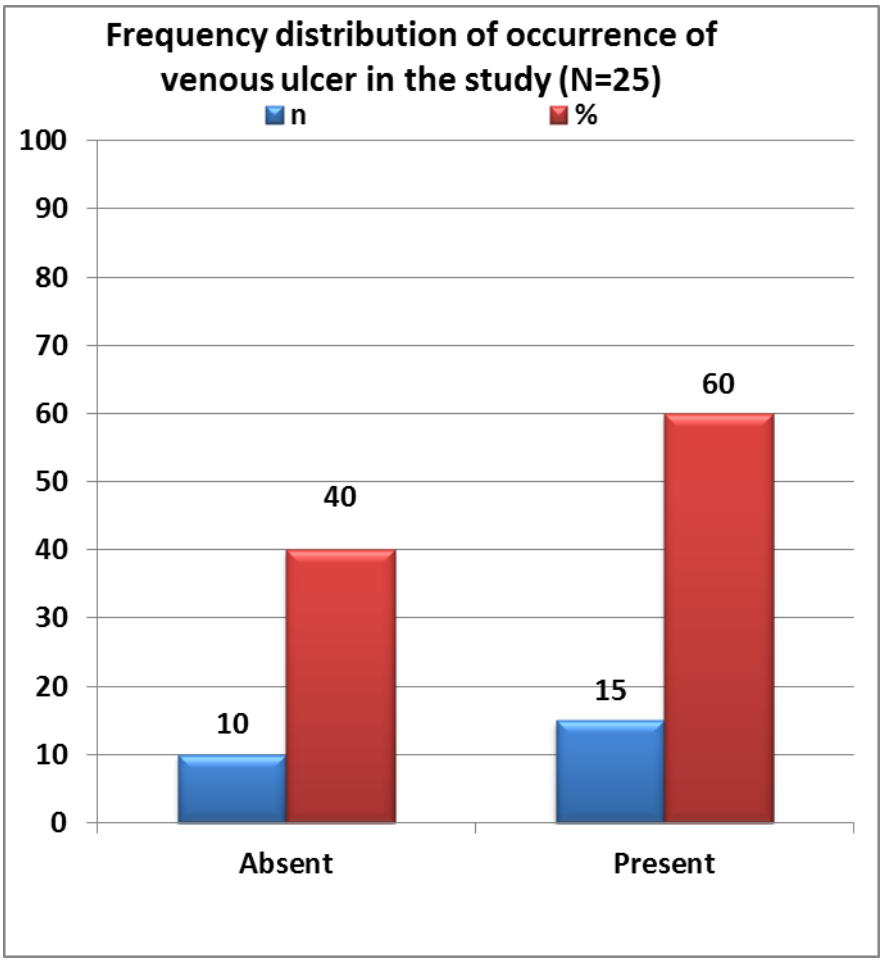


Table 6. Frequency distribution of type of severity of PTS based on Villalta score observed in the study.

Sl.No	Villalta score	n	%
1	Mild PTS	3	12
2	Moderate PTS	4	16
3	Severe PTS	18	72

Data are expressed as n with %. The total N=25.

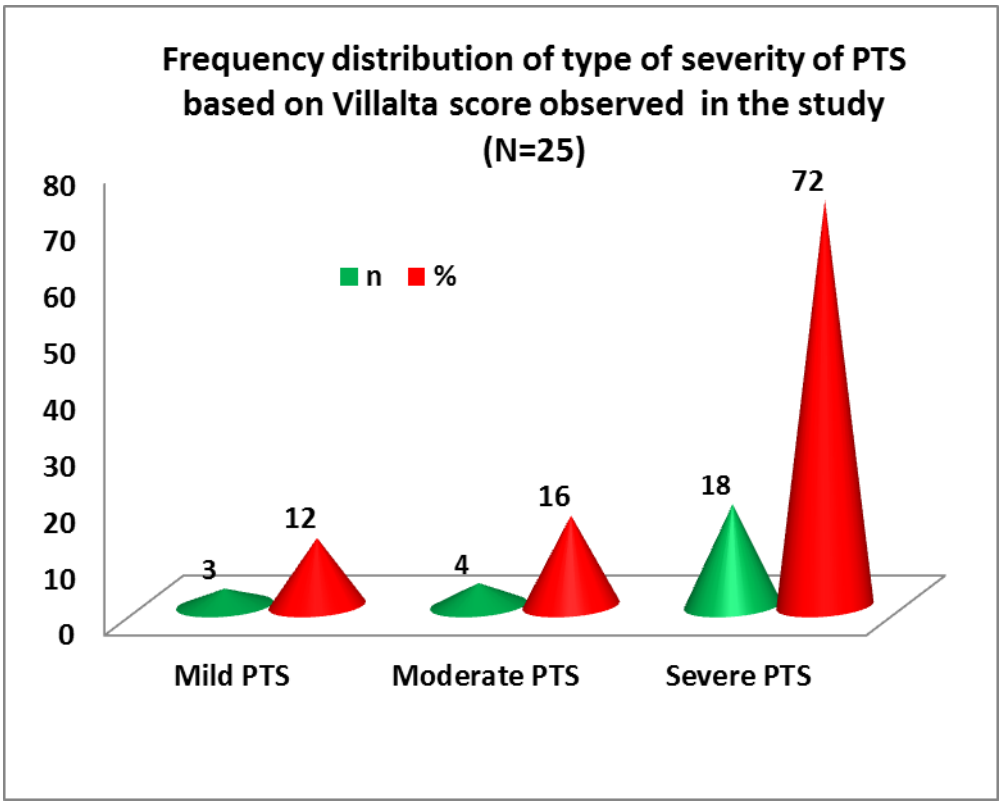


Table 7. Frequency distribution of occurrence of obesity observed in the study.

Sl.No	Obesity	n	%
1	Present	10	40
2	Absent	15	60

Data are expressed as n with %. The total N=25.

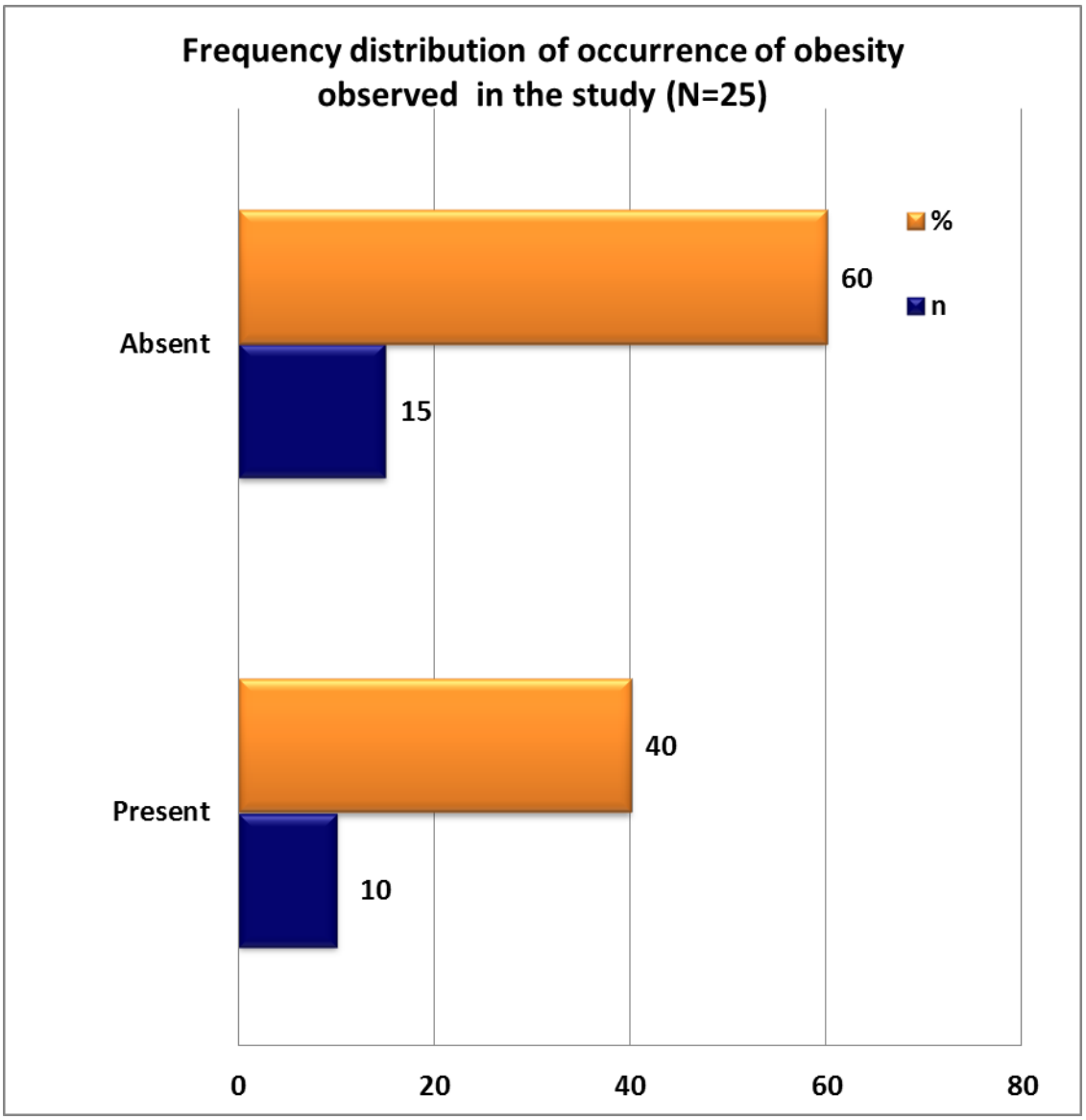


Table 8. Frequency distribution of occurrence of bleeding observed in the study.

Sl.No	Bleeding	N	%
1	Present	6	24
2	Absent	19	76

Data are expressed as n with %. The total N=25.

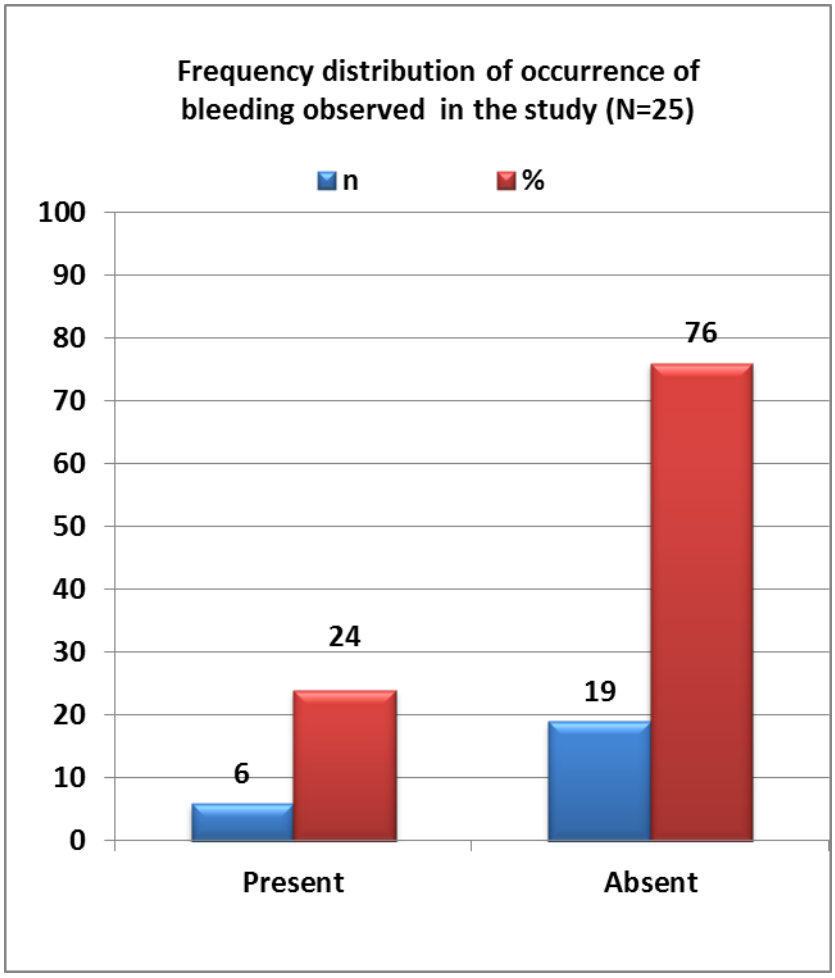


Table 9. Frequency distribution of type of DVT site observed in the study.

Sl.No	DVT site	n	%
1	Femoral vein	5	20
2	Popliteal vein	4	24
3	Femoral and popliteal veins	2	8
4	Iliac and femoral veins	5	20
5	Iliac, femoral, and popliteal veins	7	28

Data are expressed as n with %. The total N=25.

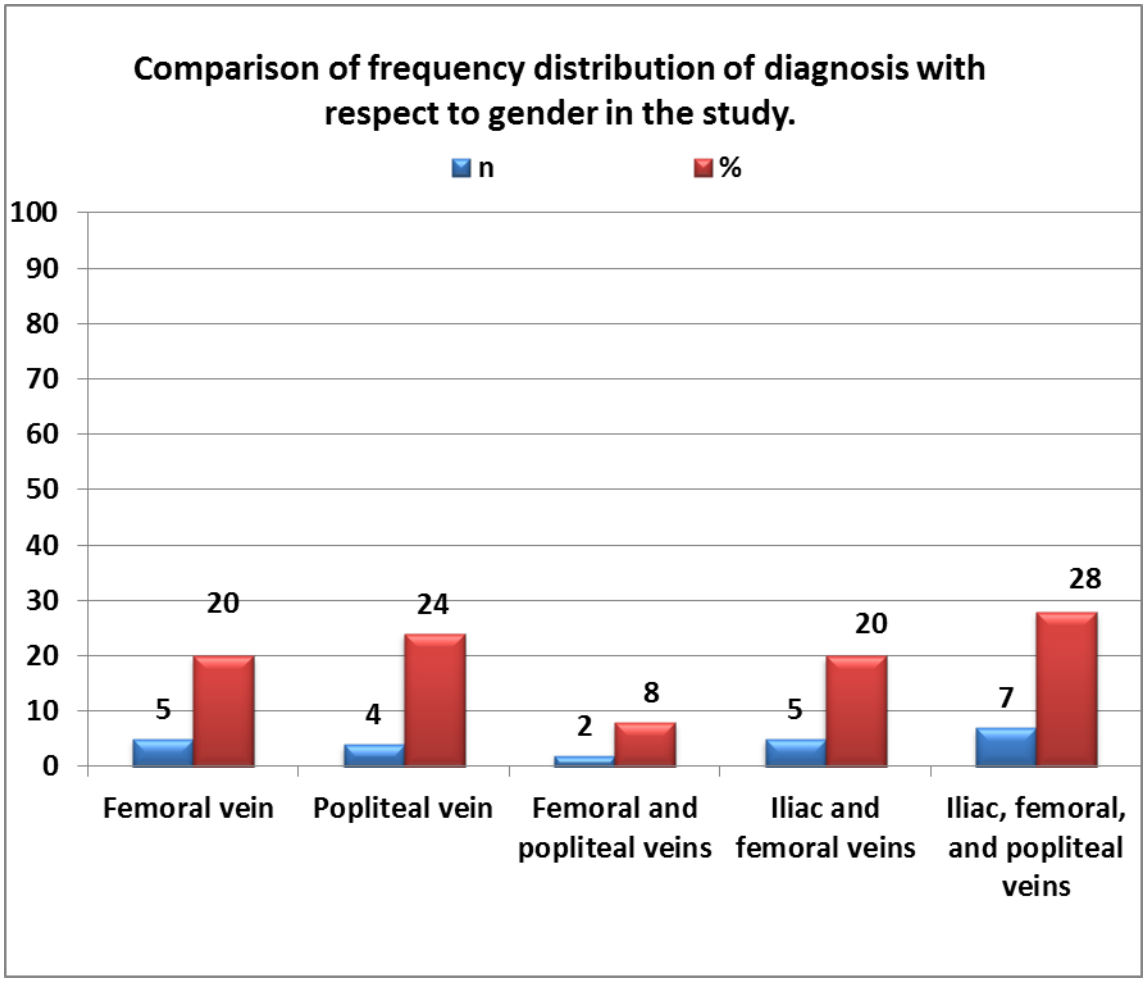


Table 10. Comparison of frequency distribution of age category with respect to gender in the study.

Sl. No	Age category	Female (n=5)		Male (n=20)		Chi square value	df	P value
		n	%	n	%			
1	20 – 40 years	0	0	12	60	5.96	2	0.049*

2	41 – 60 years	4	80	7	35			
3	>60 years	1	20	1	5			

Data are expressed as n with %. Fisher's exact test was done to compare the frequencies. *indicates $p<0.05$ and considered statistically signficant.

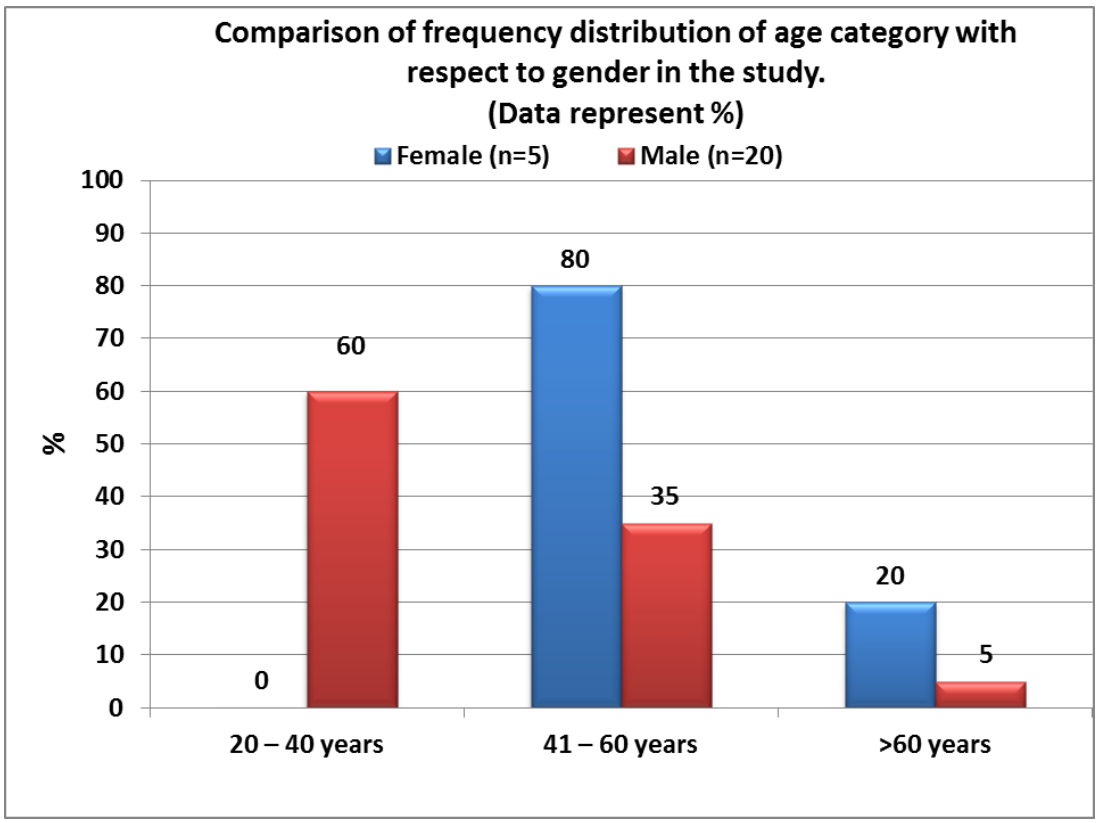


Table 11. Comparison of frequency distribution of age category with respect to ulcer development in the study.

Sl. No	Age category	No Venous ulcer	With venous ulcer (n=15)		df	P value

		(n=10)				Chi square value		
		N	%	N	%			
1	20 – 40 years	7	70	5	33.3	3.94	2	0.139 (NS)
2	41 – 60 years	2	20	9	60			
3	>60 years	1	10	1	6.7			

Data are expressed as n with %. Fisher's exact test was done to compare the frequencies. NS = Not signficant.

Table 12. Comparison of frequency distribution of age category with respect to bleeding development in the study.

Sl. No	Age category	No bleeding (n=19)		With bleeding (n=6)		Chi square value	df	P value
		N	%	N	%			
1	20 – 40 years	8	42.1	4	66.7	1.41	2	0.494 (NS)
2	41 – 60 years	9	47.4	2	33.3			
3	>60 years	2	10.5	0	0			

Data are expressed as n with %. Fisher's exact test was done to compare the frequencies. NS = Not signficant.

Table 13. Comparison of frequency distribution of various parameters with respect to gender in the study.

Sl. No	Parameters	Female (n=5)		Male (n=20)		Chi square value	df	P value
		N	%	N	%			

1	Presence of Venous ulcer	3	60	12	60	0.0001	1	>0.999 (NS)
2	Presence of bleeding	0	0	6	30	1.97	1	0.289 (NS)
3	Presence of obesity	5	100	5	25	9.37	1	0.005*

Data are expressed as n with %. Fisher's exact test was done to compare the frequencies. NS = Not signficant. *indicates $p<0.05$ and considered statistically significant.

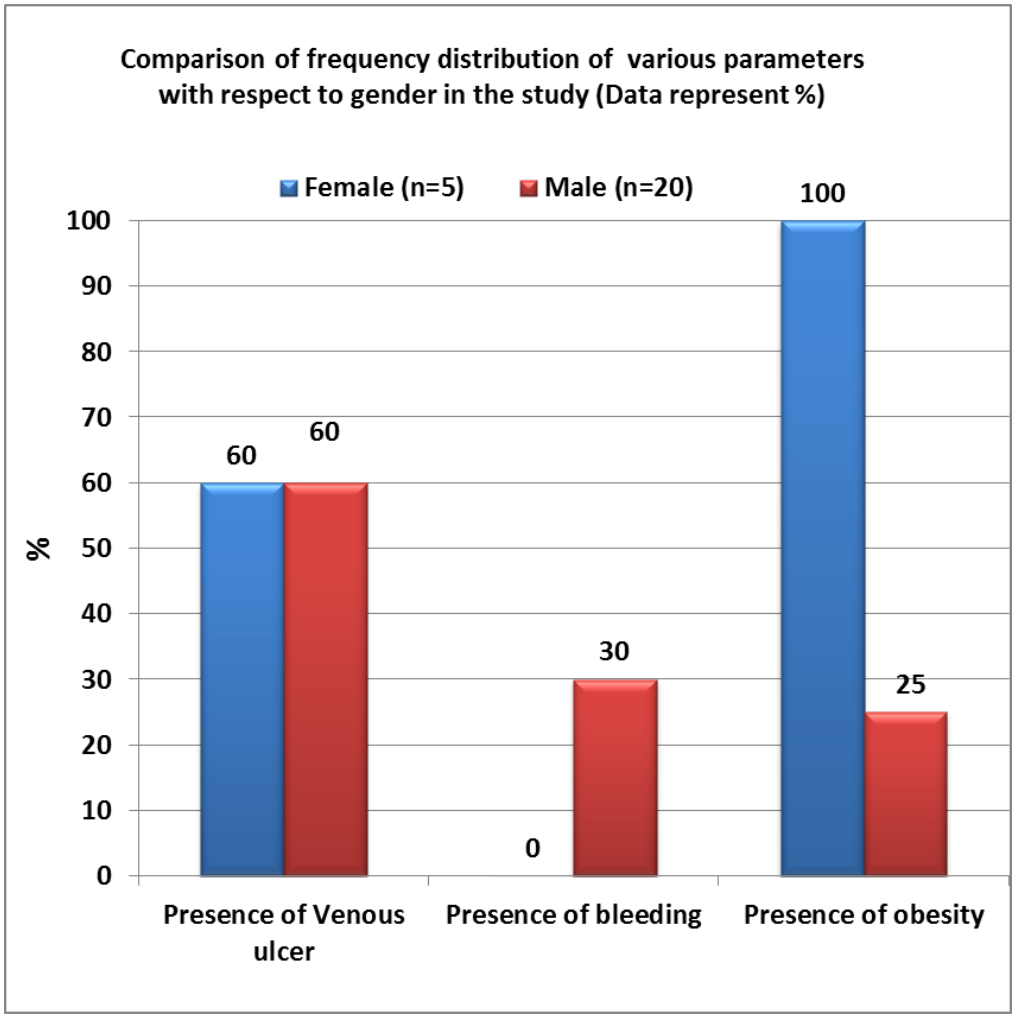


Table 14.

Comparison of frequency distribution of site of DVT with respect to gender in the study.

Sl. No	Site of DVT	Female (n=5)		Male (n=20)		Chi square value	df	P value
		N	%	N	%			
1	Femoral vein	0	0	5	25	11.6	4	0.02*
2	Popliteal vein	4	80	2	10			
3	Femoral and popliteal veins	0	0	2	10			
4	Iliac and femoral veins	1	20	4	20			
5	Iliac, femoral, and popliteal veins	0	0	7	35			

Data are expressed as n with %. Fisher's exact test was done to compare the frequencies. *indicates $p<0.05$ and considered statistically signficant.

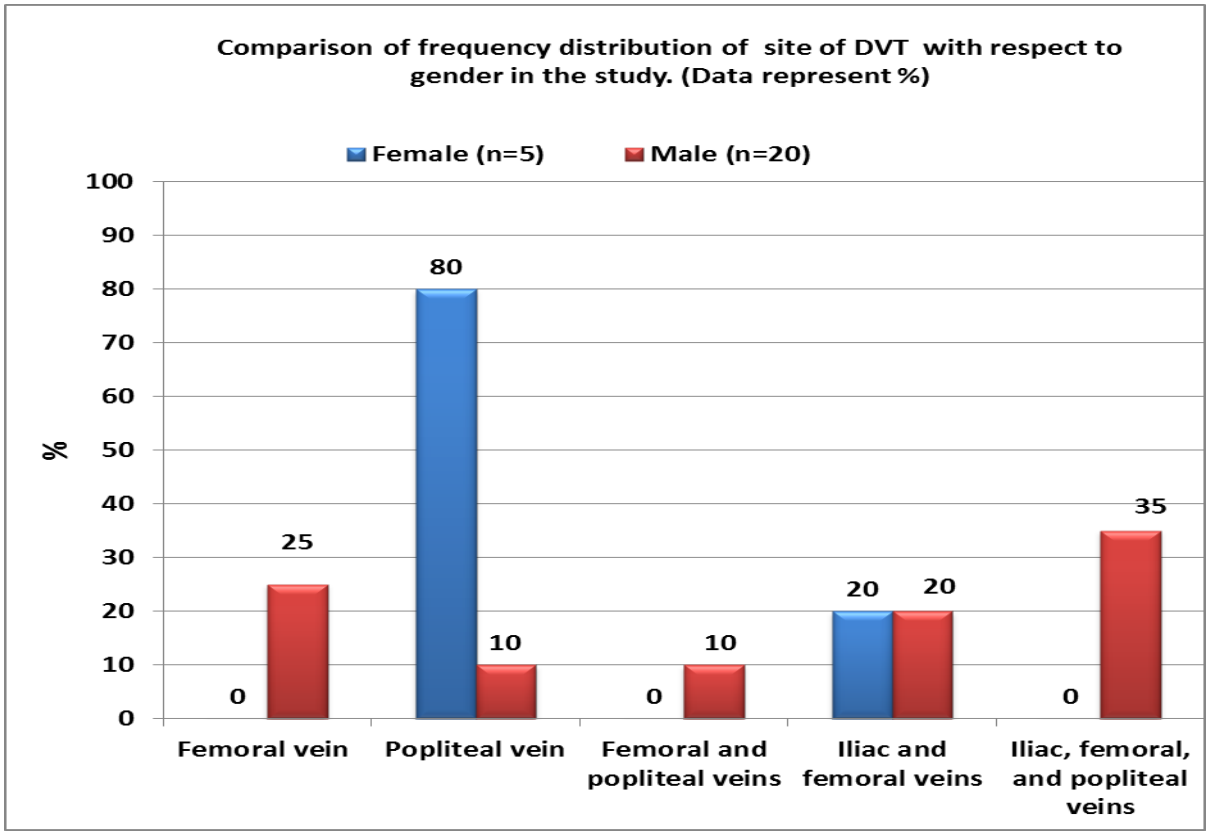


Table 15. Comparison of frequency distribution of severity of PTS with respect to bleeding development in the study.

Sl. No	Severity of PTS	No bleeding (n=19)		With bleeding (n=6)		Chi square value	df	P value
		N	%	N	%			
1	Mild PTS	3	15.8	0	0	3.07	2	0.215 (NS)
2	Moderate PTS	4	21.1	0	0			
3	Severe PTS	12	63.2	6	100			

Data are expressed as n with %. Fisher's exact test was done to compare the frequencies. NS = Not significant

Table 16. Comparison of mean duration of DVT with respect to the severity of PTS measured in the study.

Sl. No	Severity of PTS	Duration of DVT (years)			F value	df	P value
		N	Mean	SD			
1	Mild PTS	3	2.33	1.5	1.31	2, 22	0.291 (NS)
2	Moderate PTS	4	5.5	2.64			
3	Severe PTS	18	4.5	2.7			

Data are expressed as mean with SD. One-way ANOVA was used to compare the variance between the groups. NS = Not significant.

SUMMARY

This study was conducted in our institution, Thanjavur Medical College during October 2017- September 2018 to study **"the clinical spectrum of post phlebitis leg".**

25 patients in the age group of 20-70 years were included in this study. Detailed history and physical examination were done for all the patients. Basic blood investigations were done. Doppler USG was done for all the patients to confirm the diagnosis and to find out the region affected. All patients were treated with anticoagulants. Mean age group was between 21-40 years. Most common in males. Most common site was found to be ILIOFEMOROPOPLITEAL SEGMENT VEIN. 60% patients had ulcers at the time of presentation. Severity of post thrombotic syndrome is as follows mild-12%, moderate-16%, severe-72%.40% patients are with BMI >30%. Complication like active bleeding is noted in 24%. Mean duration of PTS (in years) on the basis of severity was mild – 2.33 years, moderate – 5.5 years, severe – 4.5 years.

CONCLUSION

Despite advances in DVT care in recent decades, the incidence of PTS has not decreased. Current interventions such as catheter directed thrombolysis have not proven to be unequivocally effective. ECS the long-time single and most effective form of PTS prevention is now disputed for its preventive properties, but is still valued for its role in the reduction of PTS symptomatology. So far there are no drugs specifically targeted at the prevention or treatment of PTS, and at the same time the available drugs for PTS- like symptoms in CVD such as VAD have not been sufficiently tested in patients with PTS. Ideally, PTS management should evolve from a "one treatment fits all" strategy with ECS as the only treatment modality to a more complex approach with treatment tailored to individual patients' needs. In that scenario, PTS risk prediction is based on prediction models and is followed by a multicomponent approach. Better allocation of therapy based on a uniform diagnostic strategy and risk stratification supported by risk prediction models might also improve the outcome of existing therapies. In addition, more research should be undertaken to translate pathophysiologic mechanisms of thrombus resolution and PTS development, into identification of PTS specific targets for pharmacotherapeutic intervention.

PTS is a common complication of proximal DVT. Early recognition of high-risk patients is crucial to prevent development of PTS that can be achieved by maintaining vein patency after DVT. A variety of pharmacological and

mechanical interventions have been evaluated and recommended in attempts to reduce the occurrence of PTS after acute, proximal deep venous thrombosis. Further studies are warranted to identify the optimal intervention in various patient presentations. Physician awareness of the disorder and appropriate referral to a vascular specialist are of paramount importance.

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AANEXURE-1

PROFORMA

NAME:

AGE:

SEX:

Date of examination:

Address and contact number:

Occupation-

PRESENTING COMPLAINTS with duration (Asymptomatic, Pain, Heaviness, Cramps, Numbness, Itching, Swelling of legs, Skin discolouration, Ulceration)

PAST HISTORY: history suggestive of DVT/ any surgeries of lower limb/ prolonged immobilisation.

CLINICAL EXAMINATION

Discrepancy of affected limb in comparison with unaffected limb

Skin over the limb, colour, texture, erythema, eczema, pigmentation & ulceration (number, size, site, surface, margins, edges, floor, base, scar)

Signs of ischemia (cold clammy skin, loss of hair, thinning of skin, brittle nails, marked pallor, purple blue cyanosed, ulceration of digits, wasting of muscles)

ANNEXURE-II

INFORMATION SHEET AND CONSENT FORM

Informed & written consent from patients who are attending surgical OPD in Thanjavur medical college hospital, and whom we are inviting to participate in research titled "CLINICAL SPECTRUM OF POST PHLEBITIC LEG".

Purpose of the research

Study on early identification of post thrombotic syndrome in patients who had previous episode of DVT & its subsequent management in improving the quality of life.

Type of Study

This study will involve your participation in an observational manner, with assured privacy and confidentiality.

Right to Refuse or Withdraw

Your participation is strictly voluntary. Refusal to participate will not affect subsequent services to you

Procedures

If you give consent to participate in this study, we will ask you questions regarding your illness. A history will be taken recording symptoms, duration of disease, occupation. The degree of disability is assessed by questionnaire. The

site of venous system involvement, any complications will be assessed by clinical examination. Then you will undergo standard colour Doppler ultrasonogram/ duplex venogram to find out system of involvement.

Risks

This study is purely beneficial to you with no expected risks

Benefits

Your participation will help us to define the pattern, distribution & pathological profile of post thrombotic syndrome.

Possible long-term outcome – The scoring system may assist us in determining the type of intervention & management thereby decreasing the morbidity & preventing complications.

Confidentiality

All information you provide will be kept confidential. Confidentiality will be maintained throughout the study.

ஆராய்ச்சிக்கான ஒப்புதல் கடிதம்

ஆய்வு : கால்களிலுள்ள இரத்த நாளங்களில் ஏற்படும் பாதிப்புகள் தொடர்பாக.

புறநோயாளி எண் : தேதி :

பெயர் : வயது :

இனம் : ஆண் / பெண்

இந்த ஆய்வின் நோக்கம் மற்றும் விவரங்கள் எனக்கு தெளிவாக அறிவிக்கப்பட்டது. எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்துகொண்டு நான் என் விருப்பத்தினைத் தெரிவிக்கிறேன்.

இந்த ஆய்வின் நன்மைகளைப் பற்றி மருத்துவர் மூலம் தெரிந்துகொண்டேன்.

இந்த ஆய்வில் பிறரின் நிர்பந்தமின்றி என்னுடைய சொந்த விருப்பத்தின்பேரில் பங்கு பெறுகிறேன் மற்றும் நான் இந்த ஆய்விலிருந்து எப்போது வேண்டுமானாலும் விலகிக் கொள்ளலாம் என்பதனையும் அறிந்துகொண்டேன்.

நான் என்னுடைய விருப்பத்தின்பேரில் முழு ஒப்புதலுடன் இந்த மருத்துவ ஆய்வில் என்னை சேர்த்துக்கொள்ள சம்மதிக்கிறேன்.

மருத்துவர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நாள் :

இடம் : தஞ்சாவூர்.

ANNEXURE 3 – MASTER CHART

SL NO	NAME	AGE	SEX	IP NO	VILLALTA SCORE												TOTAL SCORE	COMPLICATION	YEARS SINCE DVT	HEIGHT	WEIGHT	BMI	SEGMENT INVOLVED
					SYMPTOMS					SIGNS													
					PAIN	CRAMPS	HEAVINESS	PARESTHESIAS	PRURITIS	PRETIBIAL EDEMA	SKIN INDURATION	HYPERPIGMENTATION	REDNESS	VENOUS ECTASIA	PAIN ON CALF COMPRESSION	VENOUS ULCER		BLEEDING					
1	SENTHIL KUMAR	49	M	45688	1	1	1	1	0	0	1	2	1	2	0	+	10 +	NO	3	1.6	77	30.1	RIGHT ILIAC & FEMORAL VEIN
2	RAVI KUMAR	50	M	70350	1	1	2	1	1	1	2	2	0	1	0	+	12 +	NO	10	1.5	71	31.5	LEFT ILIAC + FEMORAL +POPLITEALVEIN
3	ARIVAZHAGAN	23	M	58233	1	0	1	1	0	1	1	2	0	2	0	-	9 +	NO	1	1.62	81	30.8	LEFT FEMORAL + POPLITEAL VEIN
4	SIVA SHANMUGAM	35	M	8262	2	1	2	1	1	1	2	2	1	1	0	+	14 +	YES	1.5	1.5	68	30.2	LEFT FEMORAL VEIN
5	SUMATHI	44	F	4303	3	3	3	2	3	2	2	3	2	2	2	+	27 +	NO	10	1.5	79	35.1	LEFT POPLITEAL VEIN
6	DHANASEKAR	50	M	5379	2	2	1	1	2	1	2	3	1	2	1	+	18 +	NO	3	1.54	67	28.3	RIGHT ILIAC + FEMORAL + POPLITEAL VEIN
7	KANAGASABAI	38	M	37177	2	1	2	2	1	1	2	3	1	2	0	+	17 +	NO	2	1.7	66	22.8	RIGHT ILIAC + FEMORAL VEIN
8	SUDHAN	27	M	51399	1	2	2	2	2	1	2	3	0	2	2	-	19 -	YES	3	1.7	72	24.9	LEFT FEMORAL VEIN
9	MOHAN	41	M	52610	1	1	2	1	1	2	2	2	0	1	0	+	13 +	YES	6	1.6	74	28.9	RIGHT ILIAC + FEMORAL + POPLITEAL VEIN
10	KARTHIK	36	M	55478	2	1	2	1	1	2	2	3	1	2	2	+	19 +	NO	3	1.58	68	27.2	LEFT FEMORAL VEIN
11	REJINA BEGAM	45	F	59708	1	1	1	1	0	1	1	2	0	1	0	-	9 -	NO	2	1.4	76	38.77	RIGHT POPLITEAL VEIN
12	MANI KANDAN	39	M	55794	1	1	2	1	1	1	1	2	1	1	0	+	12 +	NO	4	1.51	58	25.4	LEFT ILIAC + FEMORAL VEIN
13	MANI MARAN	34	M	68445	1	1	1	1	1	2	1	2	0	1	0	-	11 -	NO	8	1.6	68	26.6	RIGHT ILIAC + FEMORAL + POPLITEAL VEIN
14	VELUMYIL	32	M	46909	1	1	1	1	1	1	1	2	0	1	0	-	10 -	NO	7	1.48	66	30.1	RIGHT FEMORAL VEIN
15	PRASANNA	32	M	47389	1	1	1	1	2	1	2	2	1	1	0	-	13 -	NO	5	1.66	65	23.6	LEFT POPLITEAL VEIN
16	SARALA	45	F	45321	2	1	2	2	1	1	2	2	1	1	0	-	15 -	NO	1	1.54	74	31.2	RIGHT POPLITEAL VEIN
17	JAYA PRAKASH	63	M	46642	2	1	1	2	1	1	2	2	1	1	0	-	14 -	NO	2	1.61	54	20.8	LEFT ILIAC +FEMORAL + POPLITEAL VEIN
18	KASTHURI	70	F	64435	2	2	2	1	1	1	1	2	0	1	0	+	13 +	NO	3	1.48	68	31.1	RIGHT ILIAC + FEMORAL VEIN
19	KARTHICK	37	M	66857	2	1	2	1	2	1	2	2	0	1	0	+	14 +	YES	4	1.7	74	25.6	LEFT POPLITEAL VEIN
20	ANBAZHGAN	34	M	53328	1	0	1	1	0	1	1	2	0	2	0	-	9 +	NO	4	1.54	58	24.5	RIGHT ILIAC + FEMORAL + POPLITEAL VEIN

21	SIVA GNANAM	55	M	82062	2	1	2	1	1	1	2	2	1	1	0	+	14+	YES	3	1.58	69	27.6	LEFT ILIAC + FEMORAL VEIN
22	SUNDARI	49	F	43036	1	1	2	1	1	1	1	2	1	1	1	+	13+	NO	6	1.53	74	31.6	RIGHT POPLITEAL VEIN
23	DEENA DHAYALAN	60	M	57839	2	2	1	1	2	1	2	3	1	2	1	+	18+	NO	8	1.62	58	22.1	LEFT FEMORAL VEIN
24	KEERTHI VASAN	48	M	31254	2	1	2	2	1	1	2	3	1	2	0	+	17+	NO	7	1.54	68	28.7	LEFT FEMORAL + POPLITEAL VEIN
25	SUBRA MANIYAM	37	M	52364	1	2	2	2	2	1	2	3	0	2	2	-	19-	YES	4	1.57	58	23.5	RIGHT ILIAC + FEMORAL + POPLITEAL VEIN