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DEPARTMENT OF CLINICAL MEDICINE AND THERAPEUTICS

PREVALENCE AND SEVERITY OF POST THROMBOTIC SYNDROME AND EFFECT ON QUALITY OF LIFE AT KENYATTA NATIONAL HOSPITAL

BY

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A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTERS OF MEDICINE IN INTERNAL MEDICINE

DECLARATION

I hereby declare that this dissertation is my original work and has not been presented for the award of a degree in any other university. All materials used or quoted have been acknowledged with reference.

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DEDICATION

I dedicate this work to all Deep Venous Thrombosis patients.

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I thank Almighty God.

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ABBREVIATIONS AND ACRONYMS

BMI	Body Mass Index
CEAP	Clinical manifestations, Etiology, Anatomic distribution, Pathophysiology
CIVIQ	Chronic Venous Insufficiency Questionnaire
CVI	Chronic venous insufficiency
DVT	Deep vein thrombosis
HRQOL	Health-related Quality of Life
INR	International Normalized Ratio
ISTH	International Society of Thrombosis and Haemostasis
KNH	Kenyatta National Hospital
LMWH	Low molecular weight heparin
MEGA	Multiple Environmental and Genetic Assessment
NOAC	Novel Oral Anticoagulant
PI	Principal Investigator
PTS	Post-thrombotic Syndrome
QOL	Quality of Life
RA	Research Assistant
UFH	Unfractionated Heparin
VCS	Venous Clinical Severity
VEINES	VEnous INsufficiency Epidemiologic and Economic
VEINES QOL/Sym	VEnous INsufficiency Epidemiologic and Economic Quality of life and Symptom
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

ABSTRACT

Background: Post-thrombotic syndrome (PTS) refers to features of chronic venous insufficiency (CVI) such as pain, edema, hyperpigmentation, and venous ulcers that develop after an episode of deep vein thrombosis (DVT). There is lack of local data on the burden of PTS. The purpose of the study was to determine the prevalence and severity of PTS and to determine the impact on the quality of life (QOL) at the hemato-oncology clinics at Kenyatta National Hospital (KNH).

Methods: A cross-sectional analytical study design of adult patients with ultrasound or venogram confirmed lower limb DVT attending the hemato-oncology outpatient clinics at KNH. Patients on follow-up for at least 3 months post-DVT episode were consecutively recruited. PTS was diagnosed and graded using the Villalta Scale. Quality of life was determined using VEINES QOL/Sym questionnaire. DVT location, recurrence, prior history of varicose veins, and type of anticoagulant used were retrieved from the patient's records. PTS prevalence and severity were computed and expressed as percentages. Factors associated with PTS were determined using the Chi-square test. Independent T-test and analysis of variance were used to compare the quality of life among those with and without PTS.

Results: 1620 files of patients routinely booked to attend haemato-oncology clinics were screened for a diagnostic label and ultrasound/venogram confirmed DVT; 212 had confirmed DVT and 161 were recruited. The prevalence of PTS was 44% (N=161, 95% CI, 36 –52%). Mild PTS occurred in 51% (n=71) of participants with PTS while moderate and severe PTS was present in 22% and 27% of participants respectively. Factors associated with increased likelihood to develop PTS were: obesity (OR 3.3, 95% CI 1.4-7.5, P=0.005), history of prior ipsilateral varicose veins (OR 3.5, 95% CI 1.3-8.9, P=0.01), and Unfractionated heparin (UFH) use during the initial anticoagulation phase of DVT (OR 4.2, 95% CI 1.8-9.3, P=0.001). Participants with PTS had significantly lower QOL with VEINES-QOL mean scores compared to those without PTS (11.6; 95% CI 9.0-14.2; P <0.0001).

Conclusion: PTS is a common complication of lower limb DVT. Factors associated with an increased likelihood to develop PTS are obesity, prior history of ipsilateral varicose veins, and UFH use in early-phase anticoagulation. Patients who develop PTS had a poor quality of life.

CHAPTER ONE: INTRODUCTION

Post-thrombotic syndrome is a form of chronic venous insufficiency that can develop following an episode of DVT. PTS negatively impacts on patient's quality of life, leads to a high economic burden and it often goes undiagnosed [1,2]. Up to 50% of patients may develop PTS after an acute episode of DVT, with more than 10% experiencing a severe form despite optimal anticoagulation therapy [1]. This study aimed at determining the burden of PTS and impact on the quality of life among patients on follow-up for DVT at the KNH.

PTS has a heterogeneous clinical manifestation, ranging from chronic leg pain, swelling, peripheral neuropathy, skin hyperpigmentation, and venous ulcers in severe cases. PTS is usually diagnosed three months after an acute DVT. Although several clinical criteria can be used to diagnose PTS, the Villalta scale is widely adopted and used for diagnosis and grading [3].

The risk factors for developing PTS include advancing age, obesity, proximal location of DVT, ipsilateral recurrence of DVT, history of CVI, and suboptimal anticoagulation therapy of an acute episode of DVT [1].

Preventing initial DVT occurrence through thromboprophylaxis is a key strategy for reducing the development of PTS, however, studies show that the practice of thromboprophylaxis is suboptimal in KNH[4,5]. Once DVT has occurred, adequate duration and intensity of anticoagulation can reduce the likelihood of developing PTS. Studies from KNH show that there is suboptimal anticoagulation among patients on vitamin K antagonists [4,6]. Once PTS develops, management options are limited and can be costly. Identifying high-risk patients and providing prevention strategies for PTS is therefore crucial among patients with DVT.

Assessing health-related quality of life is an important aspect of PTS management, as it captures the patient's physical, social, and psychological well-being related to the disease. The VEINES QOL/Sym questionnaire has been validated and widely used to assess QOL among DVT patients [7,8]. PTS is associated with poor quality of life.

To the best of our knowledge, no data exist on the prevalence and severity of PTS or impact on quality of life in our setting. This study is the first to provide information on the burden of PTS at KNH.

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

The post-thrombotic syndrome describes the long-term symptoms of chronic venous insufficiency that occur after an individual has experienced an acute deep vein thrombosis [3]. PTS was previously referred to as postphlebitic syndrome. Factors that are associated with an increased likelihood to develop PTS include advancing age, obesity, prior history of CVI, ipsilateral DVT recurrence, and suboptimal anticoagulation therapy of an acute DVT.

PTS can negatively impact a patient's quality of life. Studies have shown that individuals who develop PTS have a significantly reduced health-related quality of life, similar to that of patients with conditions such as arthritis, chronic lung disease, hearing impairment, and diabetes[9–11]. The health-related quality of life of patients with severe PTS is comparable to individuals with angina, cancer, or congestive heart failure [12].

2.2 Pathophysiology of post-thrombotic syndrome

The exact pathophysiology of PTS is not yet fully understood; however, it is believed to arise from chronic venous hypertension caused by valvular incompetence and venous obstruction resulting from an acute DVT. This can lead to the accumulation of fluid and proteins in the capillaries, causing tissue edema that can progress to fibrosis and tissue ulceration [1].

Acute DVT obstructs affected venous segments, prompting an acute inflammatory response that initiates vein recanalization which may also damage adjacent valves, leading to valvular reflux resulting in exacerbation of distal venous hypertension. Valvular reflux often develops progressively, with 20% of patients experiencing it within a week of an acute DVT, 40% after a month, and 69% after a year [13].

Fibrinolysis, thrombus organization, and neovascularization are involved in the progressive recanalization of veins, which can take up to three years to complete [14,15]. If there is persistent occlusion of the venous segment affected, collateral vessels are established leading to worsening of venous hypertension. Chronic inflammation, which is often characterized by elevated interleukin 6 levels among patients with PTS, may also lead to leakage of proteinous material at the capillary beds leading to edema, lipodermatosclerosis, and ulceration [16].

There is an ongoing debate about whether obstruction or reflux is the primary mechanism responsible for PTS, although it is clear that both mechanisms are important in the development of severe PTS [17].

The interplay of the mechanisms of development of PTS is demonstrated in Figure 1.

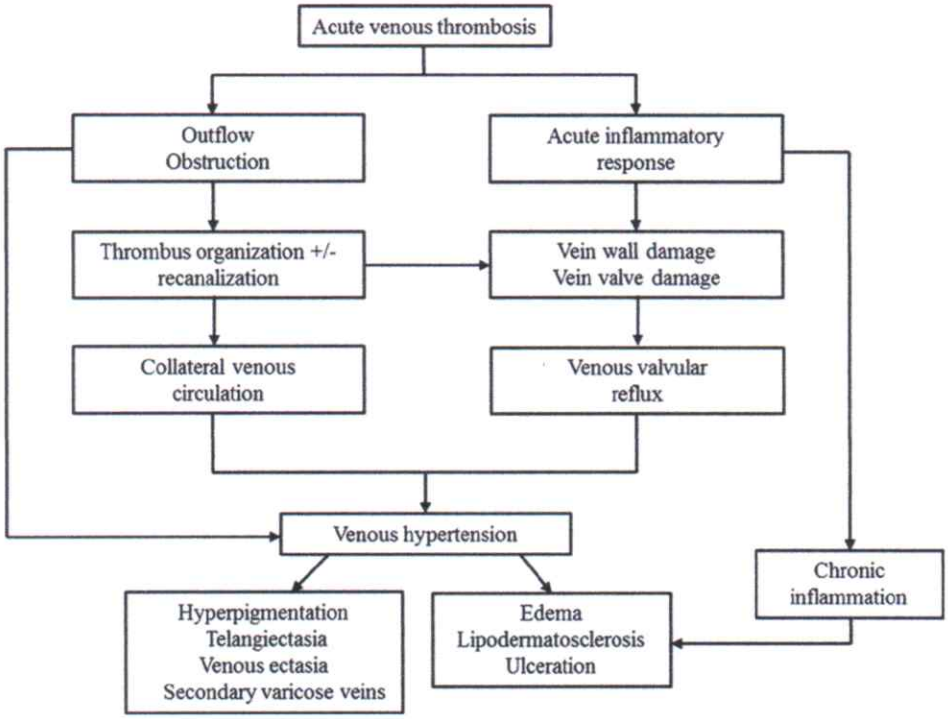

Figure 1: Pathophysiology of Post Thrombotic Syndrome (Adopted from Khan et al)[18]

2.3 Clinical features

Post-thrombotic syndrome (PTS) typically presents with symptoms and signs within three to six months of an acute lower limb deep vein thrombosis (DVT). These can include heaviness, pain, swelling, itchiness, cramps, paraesthesia, pruritus, pretibial edema, skin induration, hyperpigmentation, erythema, venous ectasia, pain on calf compression, and venous ulcers [19]. The severity and frequency of these manifestations can vary widely within individuals and over time. Rest often provides symptomatic relief while activity exacerbates symptoms. Heaviness, swelling, and pain are the most common early symptoms of PTS, while varicose veins, heaviness, and swelling are most frequently diagnosed after one year. Venous ulcers are the least common manifestation[20,21]. A retrospective study in Madagascar, done in 2020, found that

lower limb edema and varicose veins were frequent clinical signs of PTS, while lower limb heaviness was the most common symptom [22].

2.4 Clinical Tool to Diagnosis PTS

There is no definitive laboratory, imaging, or functional test that is used to diagnose PTS. In clinical practice, PTS is diagnosed based on clinical criteria. It takes up to three months for the initial DVT symptoms to resolve thus the diagnosis of PTS is considered at 3 to 6 months following an acute DVT (up to 2 years later) [1,23].

There are clinical tools that have been used to diagnose and grade PTS such as the Villalta scale, Clinical Etiologic Anatomic Pathophysiologic (CEAP) classification, Widmer classification, Venous Clinical Severity (VCS) score, Ginsberg score, Brandjes score, and recently the patient-reported Villalta scale. The CEAP classification, Widmer classification, and VCS were originally developed to diagnose and classify chronic venous insufficiencies. Despite being developed to diagnose and grade PTS, Brandjes and Ginsberg's scores have not been widely used in clinical practice and research [1,24]. The Control of Anticoagulation Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) in 2009 recommended the use of the Villalta scale to diagnose and grade PTS severity to enhance comparison between studies and for uniformity in the diagnosis of PTS[3].

The Villalta scale was developed and validated by Prandoni in 1994 (as a tool for the diagnosis and grading of PTS) in a cross-sectional study of 100 patients who were followed up six to thirty-six months following an acute DVT [25]. The score is based on five symptoms: pain, cramps, heaviness, paraesthesia, and pruritus, and six clinical signs: pretibial edema, skin induration, hyperpigmentation, redness, venous ectasia, and pain on calf compression. Each of the parameters is rated 0 if absent, 1 if mild, 2 moderate, and 3 severe and added to give a total score. Venous ulcer is graded as absent or present. A total score of more than 4 is diagnostic of PTS, with a score of 5 to 9 being mild, 10 to 14 moderate, and 15 or more or the presence of an ulcer severe PTS. Post-thrombotic syndrome is diagnosed if either there is a single score of more than four or two succeeding scores of more than four measured three months apart [1,3].

The Villalta scale has demonstrated favorable inter-rater reliability, as measured by robust kappa scores. This reliability encompasses the comprehensive assessment of clinical signs, symptoms,

and the overall Villalta scale. A sub-study of a multicenter prospective study involving 646 participants with unprovoked VTE, aimed at evaluating the inter-rater reliability of the Villalta scale among trained nursing staff responsible for the diagnosis and grading of PTS substantial reliability, indicated by a kappa coefficient of 0.71 (95% CI 0.56-0.86) [26].

The validity of the Villalta scale relies on its correlation with patient-perceived health burden and physiological indicators of PTS, given the absence of a definitive diagnostic tool. PTS is associated with poor quality of life in comparison to individuals without PTS[11,12,27,28]. PTS occurs as a result of increased venous pressures in the lower limbs, thus implying that Villalta scores should align with lower limb venous pressures. A UK-based single-center study aimed at comparing the Villalta scale with VCSS, CEAP, and venous filling pressures demonstrated that the Villalta scale demonstrated a superior correlation with venous filling pressures compared to VCSS and CEAP ($r=0$ .499; $P< 0.001$) [29]. Venous filling pressures, measured through air plethysmography, served as a proxy for lower limb venous pressures. Another study conducted in the Netherlands in 2005, involving 124 DVT patients, demonstrated a good correlation between Villalta scores and ambulatory venous pressures, with higher Villalta scores significantly associated with increased ambulatory lower limb venous pressures ($p<0.001$) [30].

The Villalta scale is widely accepted by both patients and researchers for diagnosing and grading PTS, as evidenced by its extensive use and minimal missing data. A prospective study conducted in 2008 with 387 participants reported less than 1% missing data from the Villalta scale [31].

Our study used the Villalta scale because it is easy to administer, has low user inter variability, is non-invasive, ability to diagnose and grade PTS on one assessment, and it has been used in a clinical setting similar to our study in Madagascar [22].

An important limitation of the Villalta scale is the inability to differentiate PTS from other forms of CVI and the failure to incorporate chronicity and chronology of symptoms based on acute DVT which in turn can lead to the misdiagnosis of CVI as PTS. This limitation may affect the prevalence of PTS [32,33]. Also, the lack of taking into account the chronology of an acute episode of DVT and venous ulcers makes it difficult to assess whether the venous ulcer developed after and acute DVT episode or not [3].

2.5 Prevalence and severity of Post-thrombotic syndrome

The prevalence and severity of PTS vary widely based on study designs, study populations, clinical criteria used to diagnose PTS, and time of assessment of PTS following an acute episode of DVT. Prospective studies have demonstrated that the cumulative incidence of PTS plateaus within 1-2 years of the initial DVT. However, the incidence of venous ulcers can continue to increase for up to eight years in a third of the patients who develop PTS after two years[21,34].

An observational cross-sectional study conducted in 2022 to determine the prevalence and factors associated with PTS in Sri Lanka found a prevalence of 45.5% based on the Villalta score. The study involved 80 patients attending anticoagulation clinics who had experienced acute DVT between 6 months and 2 years earlier. The majority (71%) of the participants had mild PTS, while 13.9% and 8.3% had moderate and severe PTS, respectively. Only one participant had venous ulcers. The mean age of the study participants was 50 years, 71.3% were female and the mean BMI was 25.33 kg/m^2. The factors that were significantly associated with the likelihood to develop PTS were obesity, prior history of chronic venous insufficiency, and proximal DVT location[35].

A multicenter observational study conducted in 2016 involving 504 participants diagnosed with lower limb DVT to determine the prevalence and risk factors of PTS in Spain found that 53% of the participants had PTS, with the majority (56.2%) having mild PTS, while 20.6% and 23.2% had moderate and severe PTS, respectively. The majority of the participants were male (55%) and the mean age of the participants was 61 years old. The significant factors associated with the likelihood of developing PTS were provoked DVT (immobility and hormonal therapy) and obesity [36].

A retrospective study was conducted at a teaching hospital in Pakistan in 2020 to examine predictors of quality-of-life following DVT among 125 participants diagnosed with DVT over 10 years. The participants were evaluated for PTS using the Villalta scale, and the prevalence of PTS was 39% (mild 59%, moderate 20%, severe 20%). Venous ulcers were present in 14% of the participants. The mean age of study participants was 41 years, 55% were female, 62% were obese and 21% had proximal DVT. Participants with PTS had poor QOL compared to those without PTS[11].

In 2020, a retrospective study was conducted at a teaching hospital in Madagascar to determine the epidemiology and clinical profile of post-thrombotic syndrome (PTS) among 315 patients previously admitted with lower limb DVT. PTS was diagnosed and graded using the Villalta scale and the study demonstrated that PTS was present in 34% of the participants of which 45% had mild PTS, 44% had moderate PTS and 10% had severe PTS. Among the participants with PTS, the mean age was 46 years, 72% were female, 57% were obese, 33% had recurrent ipsilateral DVT and 85% had proximal DVT [22]. Unlike the studies in Sri Lanka[35], Spain [36], and Pakistan[11], the majority of patients in Madagascar[22] had moderate to severe PTS and this could be attributed to the higher number of patients who had proximal DVT.

The prevalence of PTS, from the studies in Sri Lanka[35], Spain[36], Pakistan[11], and Madagascar [22], varies from 34% to 53% with the majority of the patients developing a mild form of PTS. Up to 23% of patients may develop severe PTS usually within 2 years following an acute DVT. Venous ulcers, the severest form of PTS, may occur in more than 10% of patients with PTS. The findings demonstrate a significant burden of PTS among patients with lower limb DVT. Among factors significantly associated with the increased likelihood to develop PTS include: obesity, prior history of CVI, proximal DVT, and provoked DVT

2.6 Risk factors for post-thrombotic syndrome

2.6.1 Age

Thrombus resolution occurs at a slower rate among older patients compared to younger patients and thus advancing age has been associated with an increased likelihood to develop PTS. Some studies have demonstrated an association between age above 60 years with the likelihood to develop PTS while other studies have not demonstrated the association. A prospective study conducted in The Netherlands in 2005, of 244 participants, found that age above 65 years was associated with 2.56 increased odds of developing PTS compared to age less than 65 years [37]. Similarly, a randomized control study in Sweden found that participants aged 60 years and above had 1.63 odds of developing PTS compared to participants below 60 years [38]. A prospective multicenter trial in Canada, of 381 patients, also found that there was a 0.3 increase in Villalta score with every 10-year increase in the age of participants[31]. In contrast, a case-control study of 1688 participants from the Multiple Environmental and Genetic Assessment (MEGA) study,

of patients with venous thromboembolism, conducted in the Netherlands in 2008 did not find an association between age above sixty years and the development of PTS [20].

2.6.2 Obesity

Obesity increases venous pressure and promotes valvular reflux in already compromised veins thus increasing the risk of developing PTS[1]. Studies have demonstrated a significant association between obesity and the development of PTS with odds ratios of up to 2.6 compared to nonobese participants [20,21,37,39]. Despite the association between obesity and the development of PTS, it is still unclear whether weight reduction decreases the likelihood to develop PTS or not[1].

2.6.3 Presence of chronic venous insufficiency

Chronic venous insufficiency leads to increased venous hypertension thus the development of PTS. The 2008 study in the Netherlands, of participants from the MEGA study, found patients with varicose veins at DVT diagnosis had a 1.5-fold increased risk of PTS compared to patients without varicose veins at DVT diagnosis [20]. A prior history of varicose veins was used to indicate the presence of CVI. A prospective study, done in Canada in 2012, to determine the predictors of PTS following the first unprovoked DVT found that CVI was associated with an increased likelihood to develop PTS (OR 2.6) [40]. Similarly, a cross-section study done in Sri Lanka in 2022 found that patients with prior history of CVI were associated with a likelihood to develop PTS compared to a lack of prior history of CVI[35].

2.6.4 Recurrent ipsilateral DVT

Recurrent ipsilateral DVT is one of the factors that have been associated with PTS development due to the worsening of the venous obstruction and subsequent increase in venous hypertension. Recurrent ipsilateral DVT occurs as a result of several factors including sub-optimal anticoagulation therapy for an acute episode of DVT. Prospective studies of patients with a first episode of DVT have demonstrated up to 2-fold risk of developing PTS compared to those without ipsilateral DVT recurrence [31,37,39].

2.6.5 Location and clot burden of DVT

Proximal DVT is defined as a thrombus involving one or more of the central veins including the popliteal, femoral, common femoral, profunda femoris, external iliac, internal iliac, and common

iliac veins, inferior vena cava whereas distal DVT is defined as a thrombus confined to one or more of the calf veins [41].

Patients with a proximal DVT location have been demonstrated to have up to two times increased odds of developing PTS compared to patients with distal DVT in prospective studies [20,35,40]. However, a cross-sectional study in Spain did not demonstrate that proximal DVT was associated with the development of PTS [36]. Besides DVT location, high clot burden has also been demonstrated to increase the likelihood to develop PTS. In two studies, patients with multisegment venous involvement of DVT were more likely to develop PTS compared to those with involvement of a single venous segment [17,42].

2.6.6 Risk factors associated with DVT treatment

Historically, heparin anticoagulation was utilized as a therapeutic approach for patients with lower DVT to prevent the onset of pulmonary embolism, recurrent DVT, and post-thrombotic ulcers [43]. The standard treatment for acute DVT usually involves administering heparin either unfractionated heparin (UFH) or low molecular weight heparin (LMWH) or novel oral anticoagulants (NOACs) during the initial phase of anticoagulation therapy. In the later phase of anticoagulation therapy for DVT, vitamin K antagonists (VKAs) or novel oral anticoagulants are typically used [44]. Regardless of the choice of anticoagulant, optimal anticoagulation therapy is paramount in reducing the risk of developing PTS.

A prospective study done in Canada on determinants of PTS among 387 participants did not demonstrate a significant association between the risk of developing PTS and early-phase DVT anticoagulation therapy with either UFH or LMWH [31]. However, long-term anticoagulation therapy of DVT using LMWH has been associated with a reduced risk of developing PTS and this is hypothesized to be due to its anti-inflammatory properties [37]. A systematic review comparing extended LMWH anticoagulation therapy and VKAs for DVT reported that LMWH was associated with significantly lower rates of PTS and a reduced incidence of venous ulcers [45].

A study done in the Netherlands in 2005, aimed at determining the association between the quality of anticoagulation treatment and the development of PTS, demonstrated that among patients treated with VKAs (target INR 2.0–3.0), those who spent more than half of the time with

a sub-therapeutic INR had an almost three-fold risk of developing PTS compared to patients who spent more than half of the time within the therapeutic INR [37]. Data from KNH shows that there is suboptimal anticoagulation among patients on warfarin with about a fifth of patients being within the therapeutic range of the INR less than half the time and the overall time in the therapeutic range of participants being about thirty percent[6]. Suboptimal anticoagulation is associated with poor thrombus resolution and thus a high risk of DVT recurrence and subsequently PTS development.

Late-phase anticoagulation therapy for DVT using NOACs can decrease the likelihood of developing PTS compared to using VKAs [46,47]. This is thought to be due to the gradual recanalization of the affected venous segment with NOACs. A post hoc analysis conducted in 2016 of 335 participants from the Einstein DVT trial (open-label, randomized trial, that compared the efficacy and safety of oral rivaroxaban alone with subcutaneous enoxaparin followed by a VKA among patients with DVT) found that patients on rivaroxaban had a slightly decreased risk of developing PTS compared to those on VKAs, although the difference was not statistically significant [46]. A retrospective study done in Brazil in 2019 showed that there was a 73% risk reduction of developing PTS among patients treated with rivaroxaban (NOAC) compared to those treated with VKAs[47].

2.7 Post-thrombotic Syndrome and Quality of Life

Quality of life is a patient-reported outcome and helps to define health in broader terms compared to morbidity and mortality. Post-thrombotic syndrome may present with persistent symptoms and thus can affect a person's working ability, have cosmetic effects, and also cause restrictions to daily living.

Several questionnaires have been used to assess health-related QOL in DVT including the VEnous Insufficiency Epidemiological and Economic Study on Quality of Life (VEINES-QOL/sym) questionnaire, Chronic Venous Insufficiency Questionnaire (CIVIQ-14), Specific Quality of life and Outcome Response Venous Questionnaire, DVT Quality of life questionnaire and Venous Thrombosis Quality of Life Questionnaire. CIVIQ-14 and VEINES-QOL/sym questionnaires are the most widely used among patients with DVT with the latter two questionnaires having not been used outside the original studies. The CIVIQ-14 questionnaire

was developed specifically to assess the quality of life among patients with chronic venous diseases [48].

VEINES-QOL/sym is a disease-specific quality of life questionnaire that was developed in a prospective multicenter study in Europe and Canada among 1531 participants as a study within the Venous Insufficiency Epidemiological and Economic Study (VEINES) group by Lamping in 2003 [49]. VEINES study aimed to describe and compare different venous leg disorders in certain aspects such as epidemiology (natural history and risk factors) and outcomes (clinical outcomes, quality of life, costs, and use of health services). The study also aimed to develop clinical tools that would be used to assess clinical outcomes among patients with chronic venous leg disorders [8].

VEINES-QOL/sym questionnaire is a twenty-six-item questionnaire with two parts assessing symptoms and quality of life. The questionnaire consists of items graded on a two to seven-point Likert scale of agreement, frequency, and intensity. It covers ten items on symptoms, nine on the limitation of daily activities, one item on the time of day with the greatest intensity, one item on change over the last year, and five items on psychological impact. Two Summary scores on symptoms and quality of life are then derived from the items excluding the time of the day with the greatest intensity which is a descriptive item. Raw scores are first transformed to z-score equivalents (mean, 0; standard deviation, 1), which then are transformed to T scores (mean, 50; standard deviation, 10) which give an easily understood range of scores. Scores for missing values are imputed using the mean amputation method. If a participant answers more than 50% of the items in a scale, a person-specific estimate can be imputed for any missing items in that scale by replacing the missing values with the mean of the observed values for that patient on that scale. Low VEINES-QOL mean scores within a sample denote a poor quality of life while high scores a better quality of life [49].

VEINES QOL/sym questionnaire was validated to assess the quality of life among DVT patients in 2005 and has since been widely used [7,11,27,28,50]. The questionnaire is self-administered and it is acceptable among patients, validated for use in patients with DVT, reliable, and responsive to clinical change (compared to generic QOL measures). VEINES QOL mean scores correlate moderately with generic QOL measures (Short-form -36 questionnaire) when assessing the quality of life among patients with DVT [7].

The post-thrombotic syndrome is associated with poor QOL scores. Studies using the VEINES QOL/Sym questionnaire have consistently demonstrated that patients with PTS report lower QOL scores than those without PTS [11,27,28]. In a study conducted in Canada, 41 patients were assessed using the VEINES QOL/Sym questionnaire, which revealed significantly lower VEINES QOL mean scores among patients with PTS compared to those without PTS (mean±SD VEINES-QOL score, 44.5±11.6 vs 54.8±5.4, P<.001). The study found a significant inverse moderate correlation between Villalta scores and mean QOL scores (r=−0.63, P<.001), indicating that severe PTS was associated with lower QOL scores[27]. However, when the generic short form 36 was used to assess QOL, no significant difference was observed between patients with and without PTS, suggesting that the difference in QOL scores was specifically related to PTS. Similar findings were reported in 2020 among a retrospective cohort of 125 participants in Pakistan, where the study demonstrated significantly lower QOL scores among patients with PTS compared to those without PTS (mean VEINES-QOL score, 42 vs 50, P<.001) and also observed a significant moderate inverse correlation between VEINES-QOL scores and Villalta scores (r=−0.617, P<.001) [11]. Additionally, a larger cross-sectional study, done in Norway in 2016, involving 254 unselected DVT patients found that those with PTS had lower QOL scores than those without PTS (VEINES-QOL mean scores (SD) 40.6(10.29) vs 54.2(5.5), P< 0.001), confirming the negative impact of PTS on QOL [28].

Several factors have been identified as predictors of QOL among DVT patients, including PTS, advanced age, high BMI, and physical inactivity [11,12].

2.8 Study Justification

The prevalence and severity of post-thrombotic syndrome (PTS) among patients with deep vein thrombosis (DVT) is a significant public health concern worldwide, with up to 50% of patients with DVT developing PTS. In Kenya, the prevalence of DVT is higher than that reported in other parts of Africa, ranging from 8.1% to 10% among patients with femur fracture and cancer patients, respectively[51–53]. Previous studies at KNH reported suboptimal thromboprophylaxis among patients admitted in the medical wards and suboptimal anticoagulation among patients on VKAs and made recommendations on studies on venous thromboembolism (VTE) outcomes to be carried out[5,6]. Despite the high prevalence of DVT and the potential for PTS, there has not

been any published data on the burden of PTS in Kenya. This study aims to address this gap by examining the prevalence and severity of PTS among patients with DVT at KNH and impact on patients' quality of life. In addition, this study will explore the risk factors associated with the development of PTS. By identifying the risk factors of PTS, this study will provide valuable information for the development of preventative strategies to improve patient outcomes. The findings of this study will form a basis of future PTS research, particularly in the face of evolving DVT management.

2.9 Objectives

2.9.1 Broad objective

To assess the burden of post-thrombotic syndrome and evaluate the impact on quality of life at KNH

2.9.2 Specific objectives

1. To determine the prevalence and severity of post-thrombotic syndrome using the Villalta scale.
2. To determine and compare health-related quality of life among patients with and without postthrombotic syndrome using VEINES QOL/Sym questionnaire.

2.93 Secondary objective

1. To determine associations between age, BMI, location of DVT, ipsilateral recurrence, prior history of ipsilateral varicose veins and type of anticoagulants used, and presence of post-thrombotic syndrome.

CHAPTER THREE: METHODOLOGY

3.1 Study Design

The study employed a cross-sectional analytical hospital-based study.

3.2 Study Area

This study was carried out at the Hematology and hemato-oncology outpatient clinics in Kenyatta National Hospital. KNH is a tertiary national hospital and the largest referral and teaching hospital in Kenya with a bed capacity of 1800. The hemato-oncology clinic runs every Monday from 8.00 am to 4.00 pm. The hematology clinic is run every Tuesday from 2.00 to 5.00 pm. Both clinics are run by consultant hemato-oncologists. The average attendance is 100 patients per clinic per week. The patients have diverse hematological conditions such as DVT, pulmonary thromboembolism, sickle cell anemia, immune thrombocytopenic purpura among others, and a variety of malignant conditions. All adult patients with DVT are followed up in the hemato-oncology clinics.

3.3 Target Population

Adult patients attending the hemato-oncology clinics with compression and Doppler ultrasound-confirmed or/and contrast venogram-confirmed lower limb DVT.

Features of DVT on Compression and Doppler ultrasound included one or more of the following features; non-compressible venous segment, loss of phasic flow on Valsalva maneuver, absent color flow (complete obstruction), lack of flow augmentation with calf squeeze, and/or increased flow in superficial veins.

Features of DVT on lower limb contrast venography were filling defects within the lower limb veins.

3.3.1 Inclusion Criteria

Patients with lower limb DVT and had been on follow-up for more than 3 months

Patients above the age of 18 years

Patients who gave consent to participate in the study

3.3.2 Exclusion Criteria

Patients with documented leg ulcers before DVT diagnosis and on follow-up for lower limb fractures or who had surgery on the same lower limb with DVT were excluded. The patients were excluded to avoid overestimation of the prevalence and severity of PTS as the Villalta scale does not take into account the chronology of events between the signs and symptoms and the occurrence of DVT.

3.4 Sample Size Determination

According to data from KNH records, 300 patients are on follow-up for DVT. A sample was drawn from this population.

To determine the prevalence and severity of PTS, the sample size was determined by Daniel's (1999) formula as illustrated [54].

$$n' = \frac{NZ^2P(1-P)}{d^2(N-1)+Z^2P(1-P)}$$

n' = sample size with finite population correction

N = Population size 300

Z = Z statistic for a level of confidence of 1.96

P = Expected proportion of PTS is 33.65% by a study by Rajaobelison et al[22]

d = Precision (in a proportion of one) of 0.05

The sample size calculated is 161.

To calculate the sample size for comparing means using a T-test between patients with and without PTS based on the mean and standard deviation values reported in the study by Kahn et al (mean±SD VEINES-QOL score of 44.5±11.6 vs 54.8±5.4) [27] sample size was calculated using the following formula [54]:

n = (Zα/2 + Zβ)2 * (σ1^2 + σ2^2) / (μ1 - μ2)^2

n = the required sample size for each group

$Z\alpha/2$ = the critical value for a two-tailed test at a significance level (α), 0.05

$Z\beta$ = the critical value for the desired power ($1-\beta$), 0.80

$\sigma 1$ and $\sigma 2$ = the standard deviations of the two groups (with and without PTS, respectively)

$\mu 1$ and $\mu 2$ = the means of the two groups (with and without PTS, respectively)

$n = (1.96 + 0.84)^2 * ((11.6)^2 + (5.4)^2) / (54.8 - 44.5)^2$

$n = 18.2$

A sample size of at least 19 patients in each group (with and without PTS) would be required to detect a significant difference in VEINES-QOL scores between the two groups:

The sample size calculated was 19 for each group those with and those without PTS.
A sample of 161 was thus used in this study as it would adequately meet both primary objectives.

3.5 Sampling Procedure

Consecutive sampling was used until the sample size was achieved.

3.6 Recruitment and Consenting Procedure

The principal investigator and research assistants went through booked patients' files in the hemato-oncology and hematology clinics record department every Monday and Tuesday respectively to identify patients with a diagnosis of lower limb DVT based on ultrasonography or venography. All the consecutive eligible patients meeting the inclusion criteria were taken through the study purpose and the consent process including the study benefits and risks, and their freedom to choose to participate in the study. The patients who gave informed consent were recruited

3.7 Definition of study outcome variables

- Post-thrombotic syndrome was defined as a Villalta score of more than four [3].

- The severity of post-thrombotic syndrome was based on Villalta scores as follows:
    - Mild PTS Villalta score of 5-9
    - Moderate PTS Villalta score of 10-14
    - Severe PTS Villalta score of $\geq$15 or the presence of an ulcer
- Quality of life
    - This was defined by mean scores from VEINES QOL/Sym questionnaire. Higher scores indicated a better quality of life and lower scores a poorer quality of life.
- Age
    - Age as a risk factor for PTS was defined as 60 years and above. Age was calculated as number of completed years based on the year of birth.
- Body mass index
    - Body mass index of more than 30kg/m^2 was considered a risk factor for PTS.
- Location of DVT
    - A proximal DVT was defined as a thrombus involving one or more of the more central veins including the popliteal, femoral, common femoral, profunda femoris, external iliac, internal iliac, and common iliac veins, and the inferior vena cava [41].
    - Distal DVT was defined as a thrombus confined to one or more of the calf veins [41]
- Recurrent ipsilateral DVT
    - Patients with documentation of a prior history of DVT on ultrasonography or venography on the ipsilateral lower limb.
- Type of oral anticoagulant
    - This was based on the type of drug or drugs that were used to treat lower limb DVT during the early and late phases of treatment including:
    - Early phase anticoagulation treatment:
        - Unfractionated heparin
        - Low molecular weight heparin
        - Rivaroxaban
    - Late-phase anticoagulation treatment:

- Rivaroxaban
- Warfarin

3.8 Data Collection Procedures

A structured study pro forma was then administered and study participants gave information on socio-demographic details such as age, gender, level of education, and employment status.

The patients' case files were used to extract details on the date of DVT diagnosis and location of DVT based on ultrasound or venography; presence or absence of recurrence of DVT; the presence of provoking factors such as malignancy, paralysis, bedridden, major surgery, pregnancy-related, oral contraception use, hormone replacement therapy. The type of anticoagulants was reviewed from the participant's case records and included unfractionated heparin, low molecular heparin, vitamin K antagonist, and direct oral anticoagulants such as rivaroxaban.

Participants' weight was measured using a calibrated scale to the nearest kilogram. The height was measured using a standard stadiometer to the nearest centimeter. BMI was calculated based on the following formula: $BMI(kg/m^2) = \frac{weight\ (kg)}{height^2(m^2)}$

The PI then determined the presence or absence of PTS and severity based on the Villalta scale (Appendix 2). This involved asking and grading for symptoms including pain, cramps, heaviness, paraesthesia, and pruritus, and then examining for pretibial edema, skin induration, hyperpigmentation, redness, venous ectasia, pain on calf compression, and presence or absence of ulcer. This was done based on the visual guide recommended for use. This was done for the limb that was affected or both in the case of bilateral DVT. The signs and symptoms were scored as 0(absent), 1(mild), 2 (moderate), or 3 (severe) based on the severity except for the venous ulcer which was scored as either present or absent. The numeric points were then summed up to yield a total score for each limb. A score of 0-4 indicated no PTS and a score of more than 4 was diagnostic of PTS. Mild PTS was scored 5-9, moderate 10-14; severe was a score of more than 15, or presence of ulceration regardless of the total score. In the case of bilateral DVT, the highest Villalta score between the two limbs was used for analysis.

Study participants were then requested to fill out the self-administered 26-item VEINES QOL/Sym questionnaire (Appendix 3). This involved answering questions about ten symptoms, nine items on limitations in daily activities, five items on psychological impact, one item on the amount of change in the respondent's leg problem over 1 year, and one descriptive item on the time of day that the leg problem was most intense. It was estimated to take 15 minutes.

Data was then checked for completeness and errors before being sent to the data entry office.

3.9 Training procedures

The research assistant was trained in data collection procedures for the study and assisted in the screening of the patients' case files for a diagnosis of DVT under the supervision of the principal investigator.

3.10 Quality Assurance

Only the principal investigator and a trained research assistant collected data. The study employed tools that have been validated to conduct this study thus not compromising the quality of collected data. Data checks and validation were done on-site to ensure accuracy.

3.11 Ethical Consideration

Approval to conduct the study was sought from the Department of Clinical Medicine and Therapeutics KNH/UON Institutional Research and Ethics Committee.

Eligible patients were enrolled in the study after an explanation was given and subsequent informed consent was signed.

Patient confidentiality was maintained at all times.

Patient-identifiable data e.g. name and hospital number were excluded from the data collection tool.

All hard copy data was stored in a lockable cabinet with access only to project staff. Soft copy data was stored under a password-protected computer, accessed only by the PI and statistician.

Patient usual care was not interrupted by this study and the results from the study were communicated back to the healthcare providers for appropriate action. Furthermore, data from this study will be used to identify the risk factors associated with the likelihood to develop PTS in our setting thus improving care to reduce PTS among patients with DVT.

Patients who declined to participate in the study were not denied standard care.

COVID-19 prevention protocol guidelines were adhered to at all times during the study period.

3.12 Data Management and analysis

Only data relevant to this study were collected in adherence to the study protocol. Collected data was checked for completeness and corrections were made on-site. Data was keyed into an electronic data entry tool designed in Microsoft Excel 2016 and then transferred to SPSS software version 26 software (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp).

Data were analyzed using both descriptive and inferential analysis. Counts and percentages were used for categorical data such as sex, DVT location, and DVT recurrence and summarized into tables and charts. Continuous variables such as age and BMI were analyzed using measures of central tendency; mean, Standard deviation, and medians.

Prevalence of PTS was calculated and expressed as a percentage of the number of participants with PTS, as assessed by the Villalta score, over the total study participants with 95% confidence intervals. The grading of the disease based on severity was calculated and expressed as a percentage of the severity (mild, moderate, or severe) over the total number of participants with PTS.

To determine the health-related quality of life, the responses on the questionnaire were entered into SPSS into the "VOL SPSS Scoring pgm REVISED NOV 07. SPS" that was provided by the developer of the questionnaire. The raw scores were converted into Z scores with a mean of 1 and a standard deviation of 0. The Z scores were then converted to T scores with a mean of 50 and a standard deviation of 10. The T scores were used to generate the mean total score, VEINES symptom score, and VEINES QOL score. Missing entries were accounted for in the scoring program by using the mean amputation method. If a participant had answered more than

50% of items in a scale, a person-specific estimate was imputed for any of the missing items in that scale by replacing the missing values with the mean of the observed values for that patient on that scale. Higher VEINES QOL scores indicated a better quality of life. Of the twenty-six items, twenty-five items were used to generate the mean score. The item on the time of the day the leg problems are more intense was a descriptive question. Independent T-test was used to compare the mean QOL among those with and without PTS and analysis of variance was used to compare mean QOL scores among the different severity ranges at a significance level of $P \leq 0.05$.

To determine the association between outcome variables bivariate analysis was employed. Data on age was categorized as above and below the age of 60 years. Data on BMI was categorized as above and below $30kg/m^2$. The chi-square test was used test for associations for the categorical data on age, BMI, DVT location, ipsilateral DVT recurrence, presence of ipsilateral varicose veins, type of anticoagulant, and likelihood to develop PTS. A p-value of ≤ 0.05 at a confidence interval of 95% would conclude a significant statistical association. Odds ratios and confidence intervals were calculated to establish the associations between PTS and risk factors.

CHAPTER FOUR: RESULTS

A total of 1620 files of patients routinely scheduled to attend the hemato-oncolgy outpatient clinics were screened for a diagnostic label of DVT between 11th October 2022 and 31st January 2023. Records of 221 patients had a diagnostic label of DVT with 212 patients' records having Compression Doppler ultrasound confirmed DVT. Of these, 51 were excluded: 23 did not attend their scheduled clinic, 12 had a duration of less than three months since DVT diagnosis, 6 had upper limb DVT, 2 were below the age of 18 years, 4 were not able to read, 3 declined consent and 1 had had ipsilateral hip surgery. One hundred and sixty-one participants were recruited into the study and included in the final analysis.

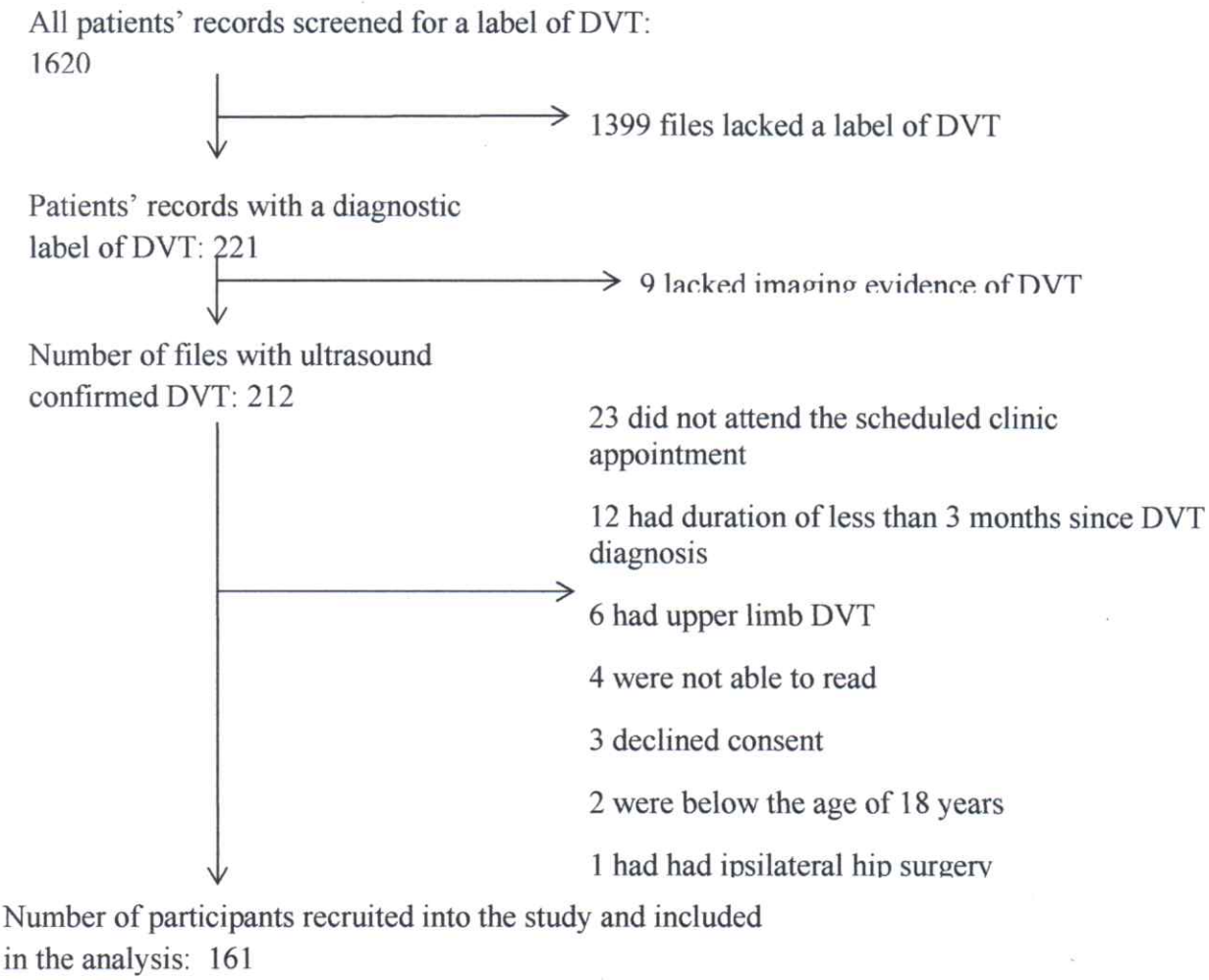

Figure 2: Recruitment flow-chart

4.1 Socio-demographic characteristics

The median age of the study participants as of study recruitment was 40 years, with a range between 18 and 70 years; 143(89%) were female, 56 (34.8%) had attained tertiary education, and 102 (63%) were employed (Table 1).

Table 1: The Socio-demographic characteristics of the participants

Variable		Median (IQR)	Frequency n(%)
Age (Years) at study		40 (39.2-52)	
	≥18-29		25(16)
	30-44		71(44)
	45-59		52(32)
	Above 60		13(8)
Sex	Male		18(11)
	Female		143(89)
Level of education attained (number of years in school)	Primary (8 years)		23(14)
	Secondary (12 years)		62(51)
	Tertiary (>12 years)		56(35)
Employment status	Unemployed		47(29)
	Employed		102(63)
	Retired		12(8)

4.2 Clinical Characteristics

The median duration of time since diagnosis of lower limb DVT was 21 months with an interquartile range of 7 to 61 months. The least duration since DVT diagnosis was 3 months while the highest was 32 years. As depicted in Table 2, 103 (64%) participants had left lower limb DVT, 45(28%) right lower limb DVT, and 13(8%) had bilateral DVT. Ilio-femoral DVT was present in 100 (62%) patients while popliteal and tibial vein DVT occurred in 44 (27%) and 17 (11%) patients respectively. A DVT-provoking factor was identified in 116(72%) participants and included pregnancy, immobility, oral contraception use, connective tissue disease, HIV infection, femoral vein catheterization, and herbal use (Table 2).

Sixty-three (39%) participants had experienced DVT recurrence among whom 50(31%) had ipsilateral lower limb DVT recurrence and 13(8%) had contralateral lower limb DVT recurrence. Twenty-three (26%) participants had a prior history of ipsilateral varicose veins.

Low molecular weight heparin was administered during early phase anticoagulation of DVT in 99 (61%) participants while unfractionated heparin and rivaroxaban were used in 34(21%) and 28(17%) respectively. Warfarin was used as a long-term anticoagulation treatment in 92 (57%) participants, while 67 (42%) participants were treated with rivaroxaban. In addition, two pregnant participants received long-term treatment with low molecular weight heparin.

The median BMI was 25.6 Kg/m^2 with an IQR was 24.1- 29.3kg/m^2. BMI ranged from 18.7 Kg/m^2 to 36.3 Kg/m^2. Thirty (19%) participants were obese with a BMI of more than 30kg/m^2.

Table 2: Clinical Characteristics of study participants

Variable		Median (IQR)	Frequencies n(%)
BMI (Kg/m^2)		25.6(24.1-29.3)	
	18.5-24.9		71(44)
	25.1-29.9		60(37)
	30 and above		30(19)
Duration since lower limb DVT diagnosis (months)		21(7-61.5)	
	3-24		89(55)
	25-60		30(19)
	61-120		25(16)
	≥121		17(11)
Lower limb DVT Site	Iliofemoral		100(62)
	Popliteal vein		44(27)
	Tibial vein		17(11)
Lower limb DVT Side	Left		103(64)
	Right		45(28)
	Bilateral		13(8)
Provoked lower limb DVT			116(72)
Provoking factors	Pregnancy/postpartum		58(36)
	Immobility		17(11)
	Oral conception use		11(7)
	Connective Tissue disease		10(6)
	HIV Infection		10(6)
	Malignancy		6
	Others		3
Unprovoked DVT			45(28)
Recurrent ipsilateral DVT			50(31)
Prior history of ipsilateral varicose veins			23(26)
Early-phase anticoagulation	UFH		34(21)
	LMWH		99(61)
	Rivaroxaban		28(17)
Long-term anticoagulation	Warfarin		92(57)
	Rivaroxaban		67(42)
	LMWH		2

UFH- Unfractionated heparin, LMWH- Low molecular weight heparin

4.3 Prevalence and Severity of PTS

Among the study participants, 71 individuals met the criteria for post-thrombotic syndrome (PTS), as indicated by a Villalta score of more than four. This represented a prevalence rate of 44% (95% CI, 36 –52%). Of the participants with PTS, 36 (51%) had mild PTS with a Villalta score of 5-9, while 16 (22%) had moderate PTS with a Villalta score of 10-14. Severe PTS, defined as a Villalta score of more than 14, or the presence of a venous ulcer, was present in 19 (27%) participants.

The PTS case-defining symptoms among individuals with PTS were lower limb pain in 56 (79%) participants and a feeling of heaviness in 53 (75%). Lower limb cramps, paraesthesia, and pruritus were reported in 49 (69%), 47 (66%), and 39 (55%) participants, respectively. On lower limbs examination, edema was present in 55 (77%) individuals, while hyperpigmentation was observed in 53 (75%). As illustrated in Figure 3, other signs of lower limb PTS included skin induration in 34 (48%), pain on calf compression in 30 (42%), lower limb venous ectasia in 18 (25%), and redness in 8 (11%) participants. A venous ulcer was present in 18 (25%) participants.

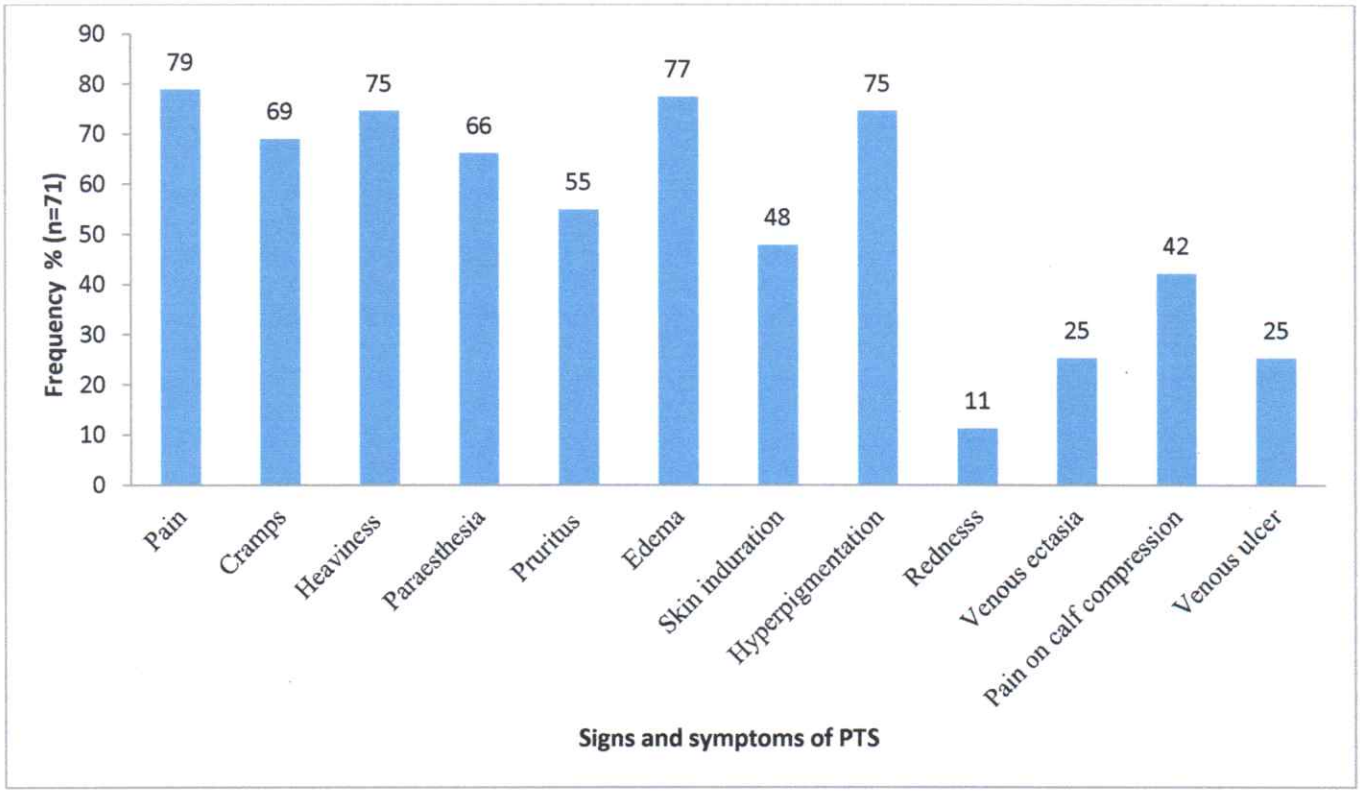

Figure 3: A bar graph showing frequencies (%) of signs and symptoms of PTS as defined by the Villalta Scale

4.4 Factors associated with the presence of post-thrombotic syndrome

Obese participants (BMI >30 Kg/m^2) had 3.3 higher odds of developing PTS compared to non-obese participants (OR 3.3, 95% CI 1.4-7.5, P=0.005). Similarly, a prior history of ipsilateral varicose veins was also found to be associated with the development of PTS compared to those who did not have a prior history of ipsilateral varicose veins (OR 3.5, 95% CI 1.3-8.9, P=0.01).

Early-phase anticoagulation with unfractionated heparin (UFH) was associated with an increased risk of PTS development, with patients treated with UFH having 4.2 (95% CI 1.79-9.28, P=0.001) higher odds of developing PTS compared to those treated with either low molecular weight heparin (LMWH).

Other factors such as age above 60 years compared to age below 60 at the time of the study, ipsilateral recurrence of DVT compared to not having an ipsilateral recurrence, proximal compared to distal location of DVT, and use of warfarin compared rivaroxaban during late phase anticoagulation were not associated with the development of PTS in this study as depicted in Table 3.

Table 3: Odds Ratios with 95% Confidence intervals from the Chi-square test showing the association of PTS with selected participants' demographic and clinical characteristics

Variable		PTS(n)	NO PTS(n)	Odds Ratio(95%CI)	P- value
Age(Years)	≥60	8	5	2.2(0.7-6.9)	0.1950
	<60	63	85		
Obesity(BMI >30Kg/m^2)	≥30	19	11	3.3(1.4-7.5)	**0.0055**
	<30	42	79		
Location of DVT	Proximal	39	61	0.6(0.2-1.4)	0.0964
	Distal	32	29		
Ipsilateral DVT recurrence	Yes	23	27	1.1(0.6-2.2)	0.7445
	No	48	63		
Prior Varicose Veins	Yes	16	7	3.5(1.3-8.9)	**0.0107**
	No	51	83		
Early Phase Treatment	UFH	24	10	4.2(1.8-9.3)	**0.0010**
	LMWH	36	63		
	Rivaroxaban	11	17	0.8(0.3-1.8)	0.5730
	Heparin	60	73		
Continuation phase treatment	Warfarin	42	50	1.2(0.6-2.2)	0.6469
	Rivaroxaban	28	39		

UFH- Unfractionated heparin, LMWH- Low molecular weight heparin

4.5 Health-related Quality of life

The VEINES QOL measure assesses the quality of life in individuals with venous disorders, including PTS, and higher scores indicate a better quality of life. The mean VEINES QOL score for participants without PTS was 55.1 (SD 7.3), while it was 43.5 (SD 9.3) for those with PTS. Among participants with PTS, the mean VEINES QOL scores for those with mild, moderate, and severe PTS were 45.6 (SD 8.1), 41.4 (SD 8.9), and 41.7 (SD 10.7), respectively, as shown in Table 4. Participants who had PTS had a poor quality of life, as evidenced by their lower VEINES QOL mean scores compared to those who did not have PTS.

Table 4: VEINES QOL mean scores, standard deviations, 95% CI, and minimum and maximum VEINES QOL scores among those with PTS and those without PTS

	N	Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum
				Lower Bound	Upper Bound		
No PTS	90	55.1	7.3	53.6	56.6	37.2	65.7
PTS	71	43.5	9.3	41.4	45.7	22.1	64.9
Mild PTS	34	45.6	8.1	42.8	48.5	25.8	56.9
Moderate PTS	16	41.4	8.9	36.6	46.1	25.2	54.0
Severe PTS	21	41.7	10.7	36.8	46.6	22.1	64.9

The mean VEINES QOL score was significantly different between participants with and without PTS (11.6; 95% CI 9.0-14.2; P <0.0001), indicating poorer quality of life for those with PTS. This difference is considered clinically meaningful, as it exceeds the minimum clinically important difference of 6 points on the VEINES QOL measure. Further analysis using one-way analysis of variance showed that there was no significant difference in mean VEINES QOL scores among the severity groups of PTS (mild, moderate, and severe) (P = 0.231).

An error bar (Figure 4) of mean VEINES QOL scores with their 95% confidence intervals show no overlap of confidence interval values among those who did not have PTS and those who had mild, moderate, and severe PTS. However, the VEINES QOL mean confidence interval values of those with mild, moderate, and severe PTS overlapped, indicating that there was no significant difference in the quality of life among the three groups.

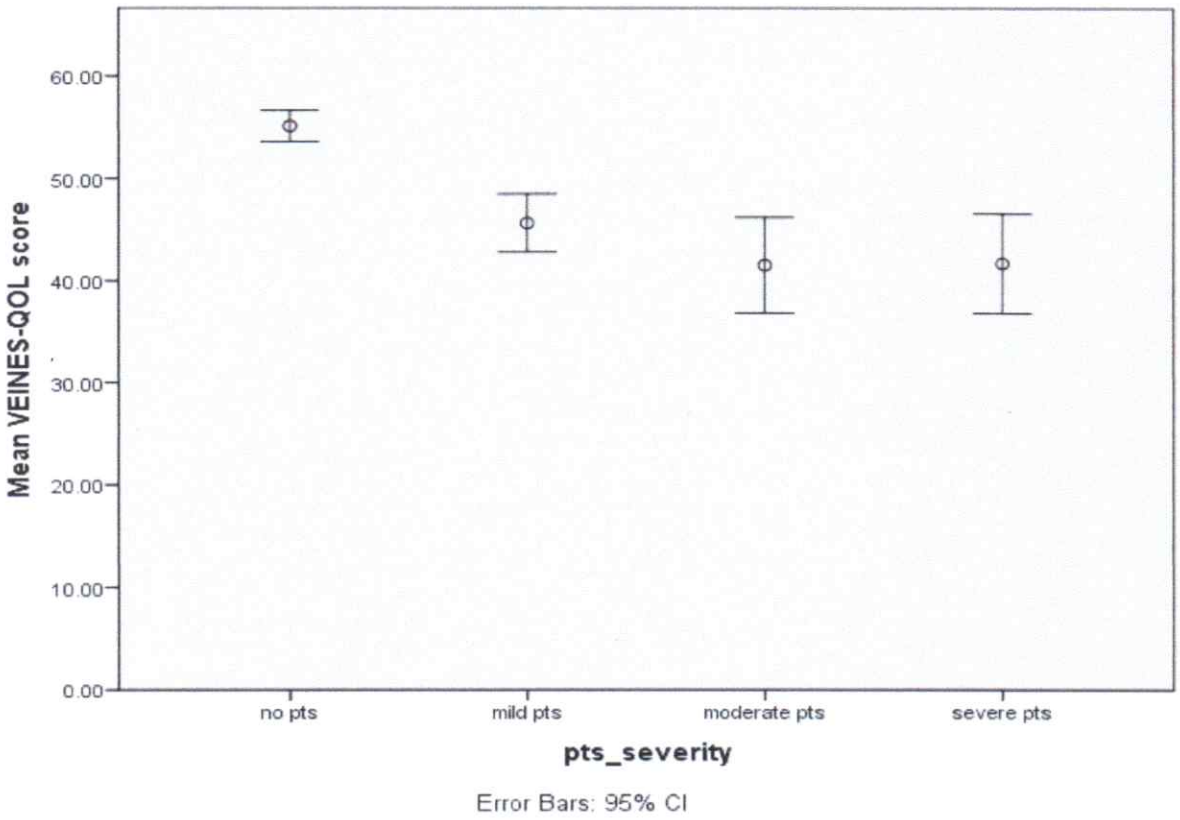

Figure 4: An Error Bar showing VEINES QOL means and 95% Confidence Interval for means among the different severities of PTS.

The scatter plot depicts an inverse linear correlation between VEINES QOL scores and Villalta scores. As the severity of the post-thrombotic syndrome, as measured by Villalta scores, increases, there is a corresponding decrease in quality of life, as indicated by lower VEINES QOL scores with an R-squared value of 0.4. This suggests that individuals with severe PTS experience a lower quality of life compared to those with mild and moderate PTS though the association is moderate and implies that 40% of a participant's quality of life was affected by PTS.

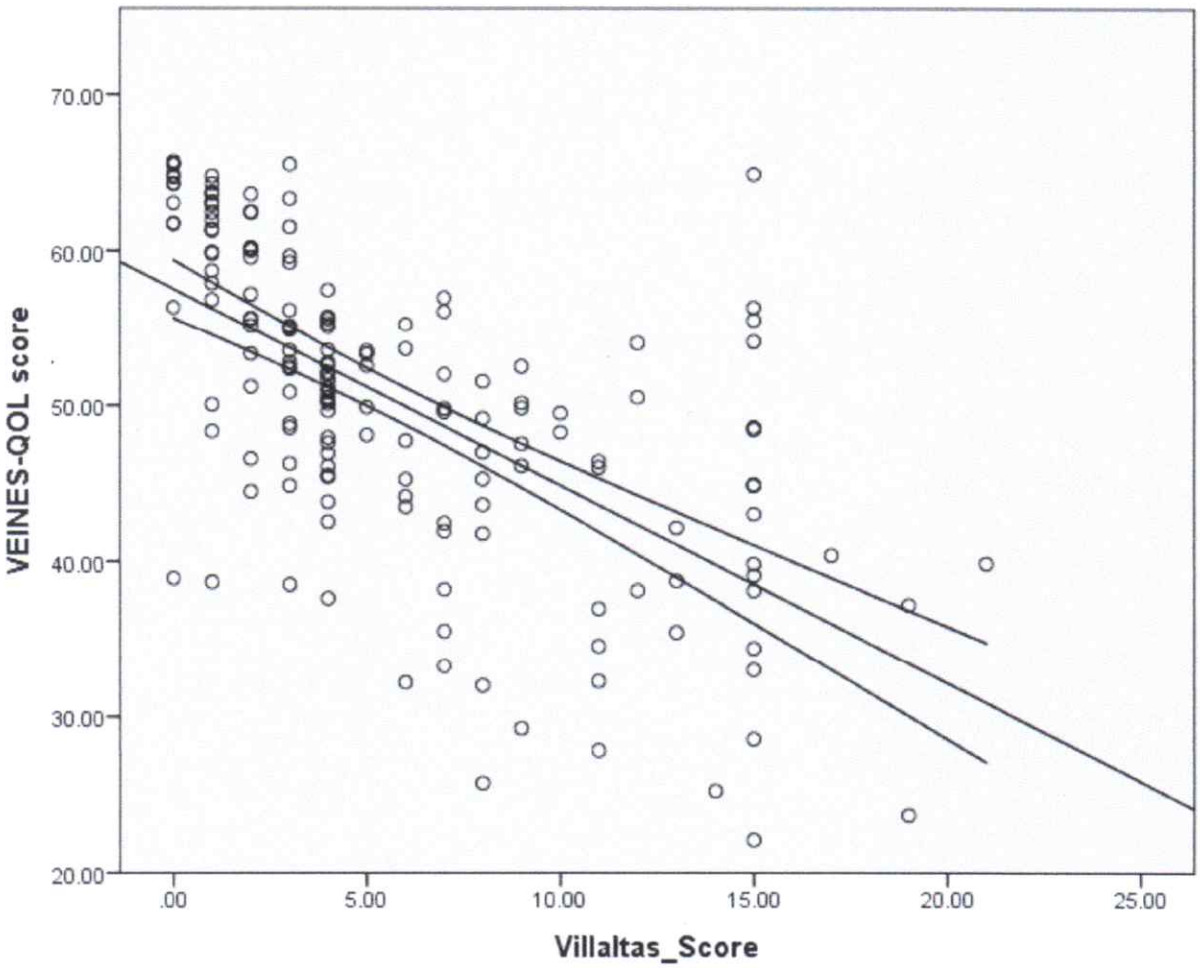

Figure 5: Scatter plot of Quality of Life score over the Villalta score with fitted values and 95% confidence interval limits ($R^2 = 0.402$)

CHAPTER FIVE: DISCUSSION

Post-thrombotic syndrome (PTS) is a sequela of deep venous thrombosis (DVT) and is characterized by symptoms of venous insufficiency. PTS has a negative impact on the quality of life of patients. This study was set to determine the prevalence and severity of PTS and effect on the quality of life of patients. The study used the Villalta Scale to diagnose and grade PTS. The point prevalence of PTS was 44% (95% CI 36%-52%). PTS severity was as follows: 51% were classified as mild PTS, 22% as moderate PTS, and 27% as severe PTS. Among the patients who develop severe PTS, over 90% have venous ulcers. The findings reflect a significantly high burden of PTS among Kenyan patients with lower limb DVT occurring at a median duration of about two years after an episode of DVT. Additionally, the population affected is fairly young with a median age of 40 years.

The prevalence of PTS in our study is consistent with findings from studies conducted in Madagascar, Pakistan, Sri Lanka, and Spain, with a reported prevalence of 33%, 39%, 45%, and 53% respectively[11,22,35,36]. Our study findings are similar to previous studies that identified mild PTS as the most common form of PTS. The similarities in the prevalence would be attributed to similar characteristics in age, gender, and participants having similar proportions of DVT recurrence and CVI. However, notably, one in every four PTS patients in our study had a severe form of PTS. A multicenter observational study in Spain conducted in 2016, with 511 participants, reported a similar severity pattern (56% mild PTS, 21% moderate, and 23% severe PTS) [35]. Similarly, a study conducted in Pakistan with 125 participants reported a similar distribution of the severity of PTS [11]. However, our study identified a higher frequency of venous ulcers (25%) compared to the study in Pakistan (14%) among participants with PTS. The higher proportion of participants with iliofemoral DVT; 62% in our study vs 21% in Pakistan, which is a known risk factor for PTS would have led to a severe form of PTS in our study[1].

A study in Madagascar in 2020 involving 315 participants found a lower frequency of severe PTS (10%) compared to our study, with mild PTS being the most common form (45%), and moderate PTS in 44% of patients [22]. Unlike our study, the Madagascar study had a lower frequency of patients with proximal DVT (62% in our study vs. 47% in Madagascar), which may have contributed to the lower severity of PTS. Ilio-femoral DVT is often associated with obstruction above the profunda vein thus impairing collateral flow and would thus lead to severe

forms of PTS in our study compared to the study in Pakistan and Madagascar. The study in Sri Lanka had fewer participants than our study, with the majority having mild PTS (91%), only 8% having severe PTS, and one patient with venous ulcers[35]. The Sri Lanka study enrolled patients diagnosed with DVT within 2 years, unlike our study, which recruited participants diagnosed with DVT for a duration ranging from 3 months to 32 years. The different severity patterns of PTS could suggest the increasing prevalence and severity of PTS over time, indicating the need for preventative measures and close monitoring of patients with lower limb DVT to reduce the burden of PTS.

Our study findings indicated that individuals classified as obese had a three-fold likelihood of developing PTS compared to non-obese participants. This association has also been observed in previous studies [20,35,37,39]. Obesity is known to increase venous pressure and cause venous valvular reflux, both of which are important mechanisms leading to the development of PTS in patients with DVT. However, there is a paucity of data regarding the effectiveness of weight loss in reducing the risk of developing PTS among patients with DVT.

Individuals with a prior history of varicose veins had a three-fold likelihood of developing PTS compared to those without such a history, which is consistent with previous studies [20,35,40]. Varicose veins are widely used as an indicator of CVI, a condition resulting from venous reflux due to valve damage that can be further exacerbated in patients with DVT. Therefore, it is imperative to manage CVI concurrently in patients with DVT to decrease the likelihood of developing PTS.

Our study found that using UFH for early-phase anticoagulation was linked to a four-fold likelihood of developing PTS compared to LMWH. Conversely, LMWH used for early anticoagulation was associated with a reduced likelihood of developing PTS in our study. In contrast, a previous study conducted in Canada did not identify any relationship between the use of either UFH or LMWH during initial anticoagulation in the management of DVT with the development of PTS [31]. However, the Canada study included patients with a first episode of proximal DVT and excluded patients who had prior CVI and randomly selected patients to use elastic compression stockings, which may have impacted the findings. Also, the study in Canada was a prospective study unlike our study which was a cross-sectional study this would have led to the differences in the findings. Both UFH and LMWH are similarly effective in treating

VTEs, but UFH has been linked to varying anticoagulation responses depending on the route of administration and thus requires frequent monitoring to ensure the appropriate dose [44]. This may be challenging to achieve in low-resource settings and thus early sub-optimal anticoagulation, which may explain why UFH was associated with an increased risk of PTS compared to LMWH in the early phase of treatment. LMWH is easier to administer, necessitates less monitoring, and has anti-inflammatory properties that may aid venous recanalization and reduce venous obstruction, ultimately reducing the risk of developing PTS [45]. There is insufficient data on studies that compare the relationship between the use of LMWH and UFH for initial anticoagulation in DVT management and the development of PTS. Our study, as well as a study conducted in the Netherlands, did not observe an association between the use of warfarin or rivaroxaban for long-term anticoagulation and the development of PTS [46]. There is still limited data on whether novel oral anticoagulants reduce the risk of the development of PTS or not and thus well-designed prospective studies would be useful in providing more information on the same.

Although our study found that individuals aged 60 years and above had a higher likelihood of developing PTS compared to those below 60 years, this association was not statistically significant. Some studies have suggested that an age of over 60 years at the time of DVT diagnosis is linked to a higher risk of developing PTS[20,37]. Moreover, prospective studies have shown that increasing age is associated with an increased likelihood of developing PTS [31,35,39]. Elderly individuals tend to have slower resorption of the clot compared to younger individuals. Age was not associated with the development of PTS likely due to the median age of our study participants being 40 years and the sample size was not powered to determine associations of PTS.

The likelihood of PTS did not increase in participants with a history of ipsilateral DVT recurrence in our study, in contrast to prospective studies done to determine the predictors of PTS [12–14]. The cross-sectional study done in Sri Lanka in 2022 on the prevalence of PTS and associated factors did not find an association between DVT recurrence and PTS similar to our findings [35]. The difference between our findings and those from the prospective studies would have been attributed to a difference in the study design. Clot burden, though not analyzed in our

study, would have contributed to our findings since a high clot burden has been associated with PTS independent of the location of the DVT [17,42].

Our study utilized the VEINES QOL/Sym questionnaire to assess the health-related quality of life (HRQOL) of patients with DVT. Our findings revealed that patients with PTS had statistically significantly reduced VEINES QOL means scores compared to those who did not have PTS (11.6; 95% CI 9.0-14.2; P <0.0001). Our findings are consistent with previous studies conducted in Canada, Norway, and Pakistan [11,27,28]. Despite differences in participant characteristics, the prevalence of PTS, and cultural and socioeconomic backgrounds, these studies all arrived at the same conclusion that PTS negatively impacts HRQOL.

PTS is a chronic condition characterized by a range of symptoms, including leg pain, heaviness, hyperpigmentation, edema, and venous ulcers in severe cases that could impair the quality of life by limiting patients' activities of daily living and working ability, as well as causing cosmetic effects. Treatment options for PTS are limited once it occurs and poses an economic burden, emphasizing the importance of preventive measures such as adequate thromboprophylaxis optimal anticoagulation once DVT occurs, as well as the use of elastic compression stockings. Our study highlights the importance of identifying and managing PTS to preserve the HRQOL of patients.

Study limitations

The study was conducted in a single-center tertiary facility and thus may not be representative of the entire population. KNH is a teaching and referral hospital that attends to referred patients across the country and may lead to an overestimation of the prevalence and severity of PTS.

Selection bias: Patients with symptoms of PTS are likely to attend the scheduled haemato-oncology outpatient clinics compared to patients without symptoms of PTS thus overestimating the prevalence and severity of PTS.

Recall bias: Patients may not have accurately recalled their symptoms and experiences, particularly since they were asked to recall symptoms over the past four weeks. Recall bias would have led to over or under-estimation of certain experiences and thus would have affected the overall quality of life mean scores.

Conclusion

Post-thrombotic syndrome is a common complication among patients with lower limb DVT. Half of the patients with PTS had moderate and severe forms of PTS. Factors associated with the likelihood to develop PTS are obesity, prior history of varicose veins, and use of unfractionated heparin during early phase anticoagulation of DVT. Patients who develop PTS after DVT have a poor quality of life.

Recommendations

Patients with lower limb DVT (especially those with known risk factors for PTS such as obesity and prior varicose veins) should be closely monitored for the development of PTS and appropriate measures should be taken to prevent PTS development and provide early treatment of PTS.

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APPENDIX 1: DATA COLLECTION TOOL

Study proforma

Study Number ☐

Sociodemographic data

1. Sex — Male ☐
   Female ☐
2. Age _____
3. Occupation — None ☐
   Employed ☐
   Retired ☐
4. Education — None ☐
   Primary ☐
   Secondary ☐
   Tertiary ☐

Clinical features

5. Duration of DVT (months) _____
6. BMI (kg/m^2) — Weight (kgs) ☐
   Height (cm) ☐
   BMI (kg/m^2) ☐
7. Location of DVT — Iliac vein ☐
   Femoral vein ☐
   Popliteal vein ☐
   Tibial vein ☐

8. Side of DVT	Left	☐
	Right	☐
	Bilateral	☐
9. Documented Provoking factor for DVT	Malignancy	☐
	Paralysis/paresis	☐
	Bedridden	☐
	Major surgery	☐
	Pregnancy /postpartum related	☐
	Oral contraception use	☐
	Hormonal replacement therapy	☐
	Others (specify) _____	
	Unprovoked DVT	☐
10. Ipsilateral DVT recurrence	Yes	☐
	No	☐
11. Prior history of varicose veins	Yes	☐
	No	☐
12. Acute treatment of DVT	Unfractionated heparin	☐
	Low molecular weight heparin	☐
	Rivaroxaban	☐
13. Long-term treatment	Warfarin	☐
	Rivaroxaban	☐

APPENDIX 2: VILLALTA'S PTS SCALE

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

APPENDIX 3: VEINES –QOL/Sym QUESTIONNAIRE

VEINES-QOL/Sym QUESTIONNAIRE

You have had a venous thrombosis. In this survey, we are interested in finding out more about the effects of your leg problem on your daily activities, both at home and at work. This information will give us a better idea about how to treat such problems.

Thank you for participating in this study. This questionnaire includes questions about your health in general and about your leg problem, as well as questions about your life and usual activities. It will take about 10 minutes to complete. All of your answers are confidential. *Do not write your name on the questionnaire.*

Thank you for your help.

INSTRUCTIONS
HOW TO ANSWER:
Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

These questions are about your leg problem(s).

1. During the past 4 weeks, how often have you had any of the following leg problems?

	(check one box on each line)	Every day	Several times a week	About once a week	Less than once a week	Never
1.	Heavy legs	☐1	☐2	☐3	☐4	☐5
2.	Aching legs	☐1	☐2	☐3	☐4	☐5
3.	Swelling	☐1	☐2	☐3	☐4	☐5
4.	Night cramps	☐1	☐2	☐3	☐4	☐5
5.	Heat or burning sensation	☐1	☐2	☐3	☐4	☐5
6.	Restless legs	☐1	☐2	☐3	☐4	☐5
7.	Throbbing	☐1	☐2	☐3	☐4	☐5
8.	Itching	☐1	☐2	☐3	☐4	☐5
9.	Tingling sensation (e.g.pins and needles)	☐1	☐2	☐3	☐4	☐5

2. At what time of day is your **leg problem** most intense ? *(check one)*

☐1 On waking
☐2 At mid-day
☐3 At the end of the day
☐4 During the night
☐5 At any time of day
☐6 Never

3. Compared to one year ago, how would you rate your **leg problem** in general now? *(check one)*

☐1 Much better now than one year ago
☐2 Somewhat better now than one year ago
☐3 About the same now as one year ago
☐4 Somewhat worse now than one year ago
☐5 Much worse now than one year ago
☐6 I did not have any leg problem last year

4. The following items are about activities that you might do in a typical day. Does your **leg problem** now limit you in these activities? If so, how much ?

	(Check one box on each line)	I do not work	YES, Limited A Lot	YES, Limited A Little	NO, Not Limited At All
a.	Daily activities at work	☐0	☐1	☐2	☐3
b.	Daily activities at home (e.g. housework, ironing, doing odd jobs repairs around the house, gardening, etc...)		☐1	☐2	☐3
c.	Social or leisure activities in which you are standing for long periods (e.g. parties, weddings, taking public transportation, shopping, etc...)		☐1	☐2	☐3
d.	Social or leisure activities in which you are sitting for long periods (e.g. going to the cinema or the theater, travelling, etc...)		☐1	☐2	☐3

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your **leg problem**?

	(check one box on each line)	YES	NO
a.	Cut down the **amount of time** you spent on work or other activities	☐1	☐2
b.	**Accomplished less** than you would like	☐1	☐2
c.	Were limited in the **kind** of work or other activities	☐1	☐2
d.	Had **difficulty** performing the work or other activities (for example, it took extra effort)	☐1	☐2

6. During the past 4 weeks, to what extent has your leg problem interfered with your normal social activities with family, friends, neighbors or groups? *(check one)*

- ☐1 Not at all
- ☐2 Slightly
- ☐3 Moderately
- ☐4 Quite a bit
- ☐5 Extremely

7. How much leg pain have you had during the past 4 weeks? *(check one)*

- ☐1 None
- ☐2 Very mild
- ☐3 Mild
- ☐4 Moderate
- ☐5 Severe
- ☐6 Very severe

8. These questions are about how you feel and how things have been with you during the past 4 weeks as a result of your **leg problem**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks -

	(check one box on each line)	**All of the Time**	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
a.	Have you felt concerned about the appearance of your leg(s) ?	☐1	☐2	☐3	☐4	☐5	☐6
b.	Have you felt irritable ?	☐1	☐2	☐3	☐4	☐5	☐6
c.	Have you felt a burden to your family or friends ?	☐1	☐2	☐3	☐4	☐5	☐6
d.	Have you been worried about bumping into things ?	☐1	☐2	☐3	☐4	☐5	☐6
e.	Has the appearance of your leg(s) influenced your choice of clothing ?	☐1	☐2	☐3	☐4	☐5	☐6

Thank you for your help.

Please write today's date: _____/_____/_____ *(day/month/year)*

APPENDIX 4: PATIENT'S GENERAL INFORMATION

Background

I am Dr Maureen Mueni Mark, a postgraduate student in the department of clinical medicine and therapeutics at the school of medicine, University of Nairobi. I would wish to inform you that am conducting a study to determine the prevalence of post-thrombotic syndrome among patients on follow-up for deep venous thrombosis.

Post-thrombotic syndrome is a chronic venous insufficiency that occurs following deep venous thrombosis and is usually characterized by pain, paraesthesia, heaviness, leg swelling, and in severe forms leg ulcers. Post-thrombotic syndrome occurs 3 to 6 months following deep venous thrombosis. It is associated with poor quality of life.

Study objective

This study seeks to determine the prevalence and severity of post-thrombotic syndrome and its impact on the quality of life in patients with lower limb deep venous thrombosis at Kenyatta National Hospital, Haematology, and haematooncology clinics.

What will happen if you decide to participate in this study?

The following will happen should you consent to participate in the study:

You will be interviewed by the principal investigator on your sociodemographic details which will be recorded on the study proforma. Details regarding DVT diagnosis and the medication you have been on will be recorded in the study proforma. Your weight will be taken using a weighing scale in kilograms and your height using a stadiometer in meters, from which your body mass index will be calculated. You will be asked about symptoms affecting your lower limbs and the principal investigator will examine both your lower limbs and the findings will be recorded in the study proforma. You will be asked to fill in a questionnaire that will assess the quality of your general health status following DVT. This is estimated to take 15 minutes of your time.

Voluntariness of participation

I would like to request you participate in this study of your free will. You will not be required to make any payments as part of this study. We will not offer you money to participate in this study. Participating in this study will not affect your usual care at the clinic.

Benefits of participating in this study

You will benefit from this study by being examined and the results will be communicated to you and your regular doctor where your treatment will be optimized.

Risks of participating

You might experience a little discomfort as your lower limbs are examined but we will be as gentle as we can to reduce the discomfort.

Confidentiality

All information collected from you will be kept confidential and will only be collected regarding this study.

Right to withdraw

You may decline to participate in this study or drop out at any time during the study. This will not lead to denial of treatment or any form of care that you are entailed to receive in the hospital If you have understood the information that I have given you and you are willing to participate in the study, I will require you to sign a form indicating your willingness to participate.

Thank you

If you have any questions concerning this study, you may contact:

Dr Maureen Mueni Mark
Senior House Officer, Department of clinical medicine and therapeutics, University of Nairobi
P.O. Box 1023-01000, Thika
TEL: +254726497946, Email: Maureenmueni@students.uonbi.ac.ke

APPENDIX 5: CONSENT FORM

STUDY TITLE: PREVALENCE AND SEVERITY OF POST THROMBOTIC SYNDROME AND ITS EFFECT ON QUALITY OF LIFE AT KENYATTA NATIONAL HOSPITAL

I _____ do confirm that I have read/ been explained the above study, understood the information presented to me, and have had the opportunity to ask questions. I understand that my participation is voluntary and that am free to withdraw from this study at any point without giving a reason.

I agree to take part of my own free will and no coercion or incentive has been offered.

Signature of participant: _____ Date: _____

Signature of investigator: _____ Date: _____

APPENDIX 6: UON/KNH ETHICS APPROVAL

UNIVERSITY OF NAIROBI
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Ref: KNH-ERC/A/400

11th October, 2022

Dr. Maureen Mueni Mark
Reg No. H58/34551/2019
Dept of Clinical Medicine & Therapeutics
Faculty of Health Sciences
University of Nairobi

11 OCT 2022
KNH-UoN-ERC

Dear Dr. Mark,

RESEARCH PROPOSAL: PREVALENCE AND SEVERITY OF POST THROMBOTIC SYNDROME AND EFFECT ON QUALITY OF LIFE AT KENYATTA NATIONAL HOSPITAL (P619/07/2022)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P619/07/2022.** The approval period is 11th October 2022 – 10th October 2023.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH-UoN ERC within 72 hours.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://research-portal.nacosti.go.ke and also obtain other clearances needed.

Yours sincerely,

DR. BEATRICE K.M. AMUGUNE
SECRETARY, KNH-UoN ERC

c.c. The Dean, Faculty of Health Sciences, UoN
The Senior Director, CS, KNH
The Assistant Director, Health Information Dept., KNH
The Chairperson, KNH- UoN ERC
The Chair, Dept. of Clinical Medicine & Therapeutics, UoN
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APPENDIX 7: SIMILARITY INDEX REPORT

PREVALENCE AND SEVERITY OF POST THROMBOTIC SYNDROME AND EFFECT ON QUALITY OF LIFE AT KENYATTA NATIONAL HOSPITAL

ORIGINALITY REPORT

9%	6%	8%	3%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	link.springer.com Internet Source	1%
2	mef.unizg.hr Internet Source	1%
3	worldwidescience.org Internet Source	1%
4	"PanVascular Medicine", Springer Nature, 2015 Publication	1%
5	M.G.R. De Maeseneer, N. Bochanen, G. van Rooijen, P. Neglén. "Analysis of 1,338 Patients with Acute Lower Limb Deep Venous Thrombosis (DVT) Supports the Inadequacy of the Term "Proximal DVT"", European Journal of Vascular and Endovascular Surgery, 2016 Publication	<1%
6	Submitted to University of Ulster Student Paper	<1%

LEAD SUPERVISOR AND CHAIRMAN'S APPROVAL

This dissertation is being submitted for the award of Masters of Medicine in Internal Medicine with the approval of my University lead Supervisor and Chairman of the Department of Clinical Medicine and Therapeutics namely:

Lead Supervisor

Professor M. D. Joshi

Associate Professor of Medicine
Consultant Physician, Cardiologist, and Clinical Epidemiologist
Department of Clinical Medicine and Therapeutics
University of Nairobi
Signature .....**Date**.....08/11/2023

Chairman Department of Clinical Medicine and Therapeutics

Professor E. O. Amayo

Professor of Medicine
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COLLEGE OF HEALTH SCIENCES
DEPARTMENT OF CLINICAL MEDICINE & THERAPEUTICS
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Signature .....**Date**.....14/11/2022