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Incidence and severity of postthrombotic syndrome after iliofemoral thrombosis – Results of the Iliaca-PTS – Registry

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Zusammenfassung – Deutsch

Das postthrombotische Syndrom (PTS) ist neben der rezidivierenden venösen Thromboembolie (VTE) und der chronischen thromboembolischen pulmonalen Hypertonie (CTEPH) eine chronische Komplikation der tiefen Venenthrombose (TVT) in den unteren Extremitäten und kann in bis zu 20–50% der Patienten innerhalb von 2 Jahren nach TVT auftreten¹⁻³. Die Prävalenz des PTS in der erwachsenen Bevölkerung wird aufgrund der zunehmenden Inzidenz von VTE voraussichtlich zunehmen. Obwohl es nicht lebensbedrohlich ist, kann es zu signifikanter Morbidität führen und sich negativ auf die Lebensqualität im Zusammenhang mit der Schwere der Erkrankung auswirken⁴⁻⁹.

Faktoren, die möglicherweise mit der Entstehung eines PTS zusammenhängen, sind das höhere Lebensalter, Fettleibigkeit, eine Vorgeschichte früherer ipsilateraler TVT, die iliofemorale Lokalisation der aktuellen Thrombose, das Versagen, sich sofort von den akuten Symptomen einer TVT zu erholen, und die unzureichende Qualität der oralen Antikoagulationstherapie^{10,11}. Darüber hinaus ist bekannt, dass der Schweregrad des PTS mit dem Ausmaß der TVT korreliert, je proximaler umso schwerwiegender sind die Folgen^{3,12}.

Ein PTS induziert eine Reihe von Symptomen und klinischen Zeichen, die in verschiedenen Skalen beurteilt werden können. Die Villalta-Skala ist eine der am besten geeigneten Skalen zur Analyse der Existenz, des Schweregrades subjektiver Symptome und der klinischen Zeichen eines PTS.

In den letzten Jahrzehnten wurden verschiedene therapeutische Strategien entwickelt, um die Mortalität aufgrund von VTE und die Langzeitmorbidität aufgrund von PTS zu verhindern¹³. Die konservative Behandlung besteht heute aus einer Antikoagulation - üblicherweise mit direkten oralen Antikoagulanzien - und einer Kompressionstherapie.

Eine der ersten invasiven Behandlungen mit dem Ziel der Thrombusentfernung war die chirurgische Thrombektomie durch Läwen im Jahr 1938¹⁴. Mahorner und Fontaine verbesserten die Technik in den 1950er Jahren und kombinierten sie mit einer gerinnungshemmenden Therapie, um einer Rethrombose und einem PTS vorzubeugen^{15,16}. Eine mechanische Thrombektomie mit Hilfe eines sogenannten Fogarty-Ballons ab 1963 oder die Schaffung einer passageren

arteriovenösen Fistel ab 1974, ebenfalls mit dem Ziel der Prävention einer frühen Rethrombose und eines PTS, werden aufgrund der hohen Invasivität, des hohen Rezidivthromboserisikos und des Risikos einer tödlichen intraoperativen Embolie heutzutage jedoch nicht mehr empfohlen^{14,17-19}.

In der gegenwärtigen Praxis beruht die frühe Thrombusentfernung hauptsächlich auf der Verwendung einer kathetergesteuerten pharmakologischen thrombolytischen Therapie²⁰. Ein weiterer Ansatz ist derzeit die endovenöse, katheter-gestützte Thrombektomie und das Stenting im Falle einer venösen Obstruktion. Es gibt eine anhaltend intensive Diskussion darüber, ob diese invasiven Therapieverfahren Patienten mit iliofemoraler Thrombose (IFT) angeboten werden sollten, was nach wie vor umstritten ist.

Das Krankheitsbild der IFT, welche das Hauptziel für die endovenöse Thrombektomie bzw. pharmakologisch-thrombolytische Therapie darstellt, ist bisher in der aktuellen Literatur nicht ausreichend vertreten, da die verwendete Definition der proximalen TVT nicht unbedingt die Iliakalvenen umfassen muß. Infolgedessen sind die Studien zu diesem Thema möglicherweise nicht repräsentativ genug, um Fragen wie Prävalenz und Schweregrad des PTS oder die Auswirkungen auf die Lebensqualität beantworten zu können.

Das vorliegende Register - das Iliaca-PTS-Register - richtet sich genau an diese Patienten und hat zum Ziel, diese Fragen zu beantworten. Die Daten von 85 Patienten, die in der Vergangenheit eine IFT erlitten hatten, wurden im prospektiven Register ausgewertet und hinsichtlich des Schweregrades des PTS, der Lebensqualität und des Auftretens eines Kompressionssyndroms der Iliakalvene bei linksseitiger IFT analysiert. Ein signifikanter Prädiktor für die Entwicklung eines schweren PTS oder einer venösen Claudicatio in unserer Patientenpopulation ist ein hoher BMI.

Die Ergebnisse dieses Registers zeigen, dass eine IFT häufig beobachtet wird und nur zehn Prozent der betroffenen Patienten ein mittelschweres oder schweres PTS bzw. eine venöse Claudicatio entwickeln. Zusammenfassend kann daher bereits eine optimierte konservative Behandlungsstrategie mit einer wirksamen Antikoagulationstherapie zu einer geringen Inzidenz von PTS und einer hohen Lebensqualität bei Patienten mit IFT führen.

Zusammenfassung – Englisch

The postthrombotic syndrome (PTS) is beside the venous thromboembolism (VTE) recurrence and chronic thromboembolic pulmonary hypertension (CTEPH) a long-term adverse outcome and chronic complication of deep vein thrombosis (DVT) in the lower extremities and can occur in up to 20–50% of patients within 2 years after DVT¹-³. The prevalence of PTS in the adult population is expected to increase due to the growing incidence of VTE in the elderly. Although not life threatening it can impose significant morbidity and can be associated with a negative impact⁴-7 on quality of life associated with disease severity³,9. From an economic point of view, PTS is an important predictor of increased health care costs after VTE.

Factors potentially related to the development of the PTS are older age, obesity, a history of previous ipsilateral DVT, iliofemoral location of the current thrombosis, failure to promptly recover from the acute symptoms and insufficient quality of oral anticoagulant therapy^{10,11}. Furthermore, it is known that the severity of PTS correlates with the location of the DVT, the more proximal the more severe^{3,12}.

PTS induces a range of symptoms and clinical signs, which can be assessed in different scales. The Villalta scale is one of the most suitable scales for defining the presence and severity of subjective symptoms and physical signs of PTS.

In the last century, various therapeutic strategies have been developed to prevent mortality due to VTE or long-term morbidity due to PTS¹³. Conservative treatment today consists of anticoagulation - usually using direct oral anticoagulants - and compression therapy. One of the first invasive treatments with the aim of thrombus removal was surgical venous thrombectomy by Läwen in 1938¹⁴. Mahorner and Fontaine improved the technique in the 1950s combining it with a course of anticoagulant treatment to prevent rethrombosis and PTS^{15,16}.

Mechanical thrombectomy by the use of Fogarty balloons, which started in 1963, or the creation of a transient arteriovenous fistula, performed since 1974, are now no longer recommended due to the high invasiveness, risk of fatal intraoperative embolism and a high rethrombosis rate^{14,17-19}.

In current practice, early thrombus removal mainly relies on the use of catheter-directed pharmacologic thrombolytic therapy²⁰. Another approach currently is the endovenous, device-driven thrombectomy and stenting in case of venous obstruction. There is an ongoing broad discussion as to whether these invasive therapies should be offered to patients with iliofemoral thrombosis (IFT), which remains controversial.

IFT, the major target for endovenous thrombectomy respectively pharmacologic thrombolytic therapy, is not enough represented in current literature because the used definition of proximal DVT does not necessarily include the iliac veins. In consequence, it may not be representative enough concerning questions like prevalence and severity of PTS or the effects on quality of life.

The present registry – the Iliaca-PTS registry – addresses exactly these patients and tries to answer these questions. The data of 85 patients who had suffered an IFT in the past were evaluated in the prospective registry documenting the severity of PTS, the occurrence of iliac vein compression syndrome in left-sided IFT and quality of life. A significant predictor for the development of severe PTS or venous claudication in our patient population is a high BMI.

The results of this registry show that IFT is frequently observed and only ten percent develop a moderate or severe PTS respectively venous claudication. In conclusion, the conservative treatment strategy with optimal effective anticoagulant therapy can lead to a low incidence of PTS and a high quality of life.

Übergreifende Zusammenfassung

Introduction

The present dissertation deals with the occurrence of post-thrombotic syndrome (PTS) as a result of iliofemoral thrombosis (IFT). The aim was, on the one hand, to determine the prevalence of IFT itself, and on the other hand the prevalence and severity of PTS as well as its influence on quality of life. To reveal predictors that could lead to severe PTS was a further aim of this work.

The causes of thrombosis are endothelial injury, stasis of blood flow and hypercoagulability and are known as the Virchow's triad. These factors favor clot formation by disturbing the balance of the opposing coagulative and fibrinolytic systems.

Pathophysiologically we devide deep vein thrombosis (DVT) in the lower limb in ascending DVT – usually starting in the calf and growing upwards by apposition, and descending thrombosis - beginning in the inferior caval or iliac vein and growing downwards into the limb. The latter is often caused by mechanical obstruction by pelvic tumors or - only on the left side - the iliac vein compression syndrome, known as May-Thurner-Syndrome (MTS). Obstruction of the iliac veins is assumed to lead to severe PTS.

DVT can lead to chronic venous hypertension via two principal mechanisms: persistent (residual) venous obstruction and valvular reflux. After DVT, recanalization of the thrombosed veins, which occurs through a combination of fibrinolysis, thrombus organization, and neovascularization, is often incomplete, resulting in venous obstruction. Damage to venous valves leading to valvular reflux probably occurs by thrombus-induced activation of inflammation, fibrous scarring associated with acute and resolving thrombosis, or venous dilation distal to the obstructed venous segment. These findings provide the basis of the 'open vein hypothesis', which postulates that early thrombus elimination and restoration of venous flow might prevent PTS after proximal DVT⁴.

The exact prevalence of IFT as a major risk factor for the development of PTS is not known in the population. In the recent literature, exact prevalence data concerning IFT are lacking. Previous publications on PTS referred to proximal DVT, which did not necessarily include iliac vein involvement. MTS may be one of the major risk factors for developing left-sided IFT, but the prevalence of MTS in patients with IFT is still unknown due to difficulties in diagnosing MTS.

Therapy decisions and recommendations such as revascularizing treatments of IFT are mainly based on recent literature. And even in the current literature there is an ongoing controversial discussion whether medical or revascularizing treatment methods can prevent severe PTS²⁰⁻²².

The German S2k-AWMF-Guideline "Venenthrombose und Lungenembolie: Diagnostik und Therapie" in the current version from 2015 recommends, that revascularizing treatment of IFT can be applied, if indicated, as soon as possible, to prevent PTS (s. https://www.awmf.org/leitlinien/detail/ll/065-002.html).

Presentation of the publication

We have performed a retrospective single-center registry with patients presenting with DVT and IFT in the CCB vascular center in Frankfurt / Germany between 2014 and 2017. In the following we set up a prospective registry in which 85 patients with IFT could be included for further analysis (Table 1).

The index event had occurred on average 4 years before the time of the investigation. 52.9% (45/85) were female and the median age was 40.0 years. Median Body-Mass-Index (BMI) was 27 kg/m².

76.5% (65/85) had a left-sided IFT, 15.3% (13/85) had a right-sided IFT, and 8.2% (7/85) presented with bilateral IFT. In 53.8% (35/65) of patients with left-sided IFT, May-Thurner syndrome (MTS) was suspected. Descending IFT occurred in 69.2% (45/65) of patients with left-sided IFT and 77.8% (35/45) of these were diagnosed with MTS.

27.1% (23/85) of patients with IFT had undergone surgical, interventional or catheter-directed thrombolytic (CDT) therapy while 72.9% (62/85) had received conservative treatment (anticoagulation and compression stockings).

Patients in the interventional group were significantly younger (median age 34.0 vs. 46.5 years) and presented more often with MTS (77.8% vs. 44.7%).

Table 1: Baseline characteristics of patients with IFT in the Iliaca-PTS registry

	All	Conservative	Interventional	p-value
	n=85	therapy	therapy	
		n=62	n=23	
Age; median [min-max]	40.0 [15-76]	46.5 [15-76]	34.0 [16-59]	0.021
Female; n (%)	45 (52.9)	32 (51.6)	13 (56.5)	0.808
BMI; median [min-max]	27 [19-46]	27 [19-46]	25 [20-44]	0.414
BMI 18.5 – 24.9; n (%)	27 (31.8)	17 (27.4)	10 (43.5)	0.269
BMI 25 – 29.9; n (%)	37 (43.5)	30 (48.4)	7 (30.4)	
BMI ≥ 30; n (%)	21 (24.7)	15 (24.2)	6 (26.1)	
Period of time (years)	4 [0-20]	3 [0-20]	5 [1-17]	0.363
between occurrence of				
IFT and examination;				
median [min-max]				
IFT right-sided; n (%)	13 (15.3)	12 (19.4)	1 (4.4)	0.058
IFT both-sided; n (%)	7 (8.2)	3 (4.8)	4 (17.4)	
IFT left-sided; n (%)	65 (76.5)	47 (75.8)	18 (78.3)	
IFT left-sided with MTS;	35 (53.8)*	21 (44.7)*	14 (77.8)*	0.025
n (%)				
"Ascending" IFT; n (%)	26 (30.6)	21 (33.9)	5 (21.7)	0.427
"Descending" IFT; n (%)	59 (69.4)	41 (66.1)	18 (78.3)	

^{*}Based on Patients with Left-sided IFT; BMI: Body-Mass-Index (kg/m²); IFT: Iliofemoral

Thrombosis; DVT: Deep Vein Thrombosis; MTS: May-Thurner Syndrome.

The majority of patients with IFT had no or mild PTS; moderate or severe PTS was observed in every tenth patient while none of them had developed a venous ulcer at any time (Figure 1).

Quality of Life in the overall study population was high, Comparison of the VEINES Scores revealed no significant difference between the conservative and the interventional treatment group (Table 2).

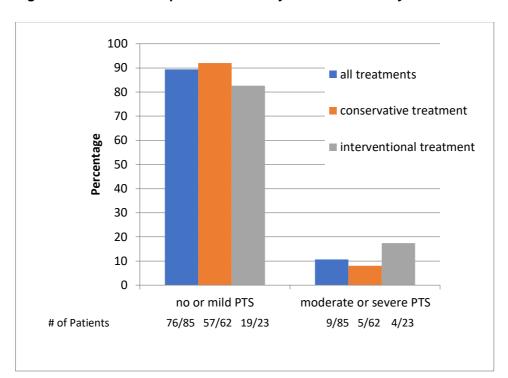


Figure 1: Occurrence of postthrombotic syndrome defined by Villalta Score

PTS: postthrombotic syndrome; No or mild PTS: Villalta Score < 10; moderate or severe PTS: Villalta Score ≥10.

Table 2: Results of the Quality of Life – VEINES Scores (higher score indicates better outcome), Wilcoxon-Mann-Whitney-U-Test

VEINES-Scores	All	Conservative	Interventional	p-value
	n=85	n=62	n=23	
Clinical Symptoms				
(VEINES-Sym score)	41 [14-48]	40.5 [14-48]	41 [20-46]	0.448
median [min-max]				
Quality of life				
(VEINES-QOL score),	46 [24-57]	46.5 [24-57]	45 [24-57]	0.452
median [min-max]				
Combined VEINES-QOL/Sym				
score	86 [38-103]	88 [38-103]	83 [51-103]	0.839
median [min-max]				

A high BMI was identified to be a significant predictor for developing a moderate or severe PTS (VS ≥ 10) and venous claudication in IFT patients which is in

accordance with the current literature. None of our registry patients had developed a venous ulcer.

Discussion

Although the most common location of DVT is a femoropopliteal or distal thrombosis, iliofemoral thrombosis was diagnosed in nearly every fifth patient of the examined population with DVT. Additionally, in the majority of patients the IFT was located on the left side. Left sided descending IFT was associated with MTS, which suggests that MTS might be one of the major risk factors for the development of this type of IFT. Although many uncertainties exist regarding the prevalence of MTS and its pervasiveness in DVT our registry provides for the first time a systematic analysis of the possible relationship between left sided descending IFT and MTS as a possible reason.

Reported prevalences of PTS after DVT differ widely among other studies because of differences in study populations, tools used to assess PTS and time interval between acute DVT and PTS assessment. Up to 10% will develop severe PTS. So far it has been assumed that the risk of developing moderate or severe PTS is increased in patients with IFT compared to patients with proximal lower limb DVT excluding the iliac veins or compared to infrapopliteal DVT. In our registry, the majority of patients with IFT had no or mild PTS and moderate or severe PTS was observed in every tenth patient while none of them had developed a venous ulcer at any time.

As one can expect, we could demonstrate in our registry that the grade of PTS had a significantly high negative impact on the quality of life. Therefore avoidance of severe PTS is one of the major goals to increase quality of life after occurrence of IFT in this patient population. In our prospective registry nearly every third patient received interventional treatment. These patients were younger on average and presented mainly with left sided IFT and MTS. The incidence of PTS of the interventional treated patients was comparable to the conservatively treated patients.

Existing literature is controversial concerning the question, if either early thrombus removal or medical treatment might be able to prevent severe PTS. The CAVA- and the ATTRACT-trial showed no significant differences between

both treatments, whereas the CaVenT-trial revealed a lower incidence of PTS in the interventional group compared to the standard treatment group²⁰⁻²².

One could cautiously conclude that with conservative therapy the results with regard to the occurrence of a postthrombotic syndrome may not be as poor as described in literature and possibly only a few patients might benefit from revascularization. One could further discuss that based on our data it could probably be more beneficial to wait a certain time before revascularization in case of fresh descending thrombosis, whether the conservative therapy is effective and only to revascularize the minority of patients who after 6 Months are still severely symptomatic.

Prospective trials with randomization for interventional or conservative treatment in case of acute IFT explicitly including the iliac veins are needed. These results will help to decide whether acute interventions can improve the outcome of PTS in this patient population. Since the majority of patients with conservatively treated IFT present with no or mild symptoms of PTS, patients with moderate to severe PTS and/or venous claudication might profit most from modern interventional strategies. Also patients with a phlegmasia coerulea dolens, which is a severe limb-threatening complication of an acute IFT should be treated interventionally.

Übersicht der zur Veröffentlichung angenommenen Manuskripte bzw. Publikationen

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Publikation

Original communication



Incidence and severity of postthrombotic syndrome after iliofemoral thrombosis – results of the Iliaca-PTS – Registry

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Summary: Background: Deep venous thrombosis (DVT) and in particular, iliofemoral thrombosis (IFT) can lead to recurrent thrombosis and postthrombotic syndrome (PTS). Data on the prevalence, predictors and outcome of IFT are scarce. Patients and methods: We retrospectively searched our database of outpatients who had presented with DVT and IFT including the iliac veins from 2014 until 2017. In addition, we performed a prospective registry in a subgroup of patients with IFT. These patients received duplex ultrasound, magnetic resonance venography and measurement of symptom-free walking distance using a standardized treadmill ergometry. The severity of PTS was analyzed using the Villalta-Scale (VS) and quality of life was assessed using the VEINES-QOL/Sym Questionnaire. Results: 847 patients were retrospectively identified with DVT and 19.7% (167/847) of these presented with IFT. 50.9% (85/167) of the IFT-patients agreed to participate in the prospective registry. The majority of these patients (76.5%: 65/85) presented with left-sided IFT. In 53.8% (35/65) May-Thurner syndrome was suspected. 27.1% (23/85) underwent invasive therapy. Moderate or severe PTS (VS \geq 10) occurred in 10.6% (9/85). The severity of PTS is correlated with a reduced quality of life (ρ (CI 95%) = -0.63 (-0.76; -0.46); $\rho < 0.01$). None of the patients presented with a venous ulcer at any time. A high body mass index was a significant predictor (OR (CI 95%) = 1.18 (1.05; 1.33), $\rho = 0.007$) for the development of clinically relevant PTS (VS \geq 10) and venous claudication. Conclusions: Every fifth patient with DVT presented with an IFT. The majority developed left sided IFT. Every 10th patient developed moderate or severe PTS (VS \geq 10). A high body mass index was predictive for the development of PTS and venous claudication.

Keywords: Deep vein thrombosis, iliofemoral thrombosis, postthrombotic syndrome

Introduction

Postthrombotic syndrome (PTS) is a chronic complication of deep vein thrombosis (DVT) in the lower extremities and can occur in up to 20–50% of patients within 2 years after DVT [1-3]. It can impose significant morbidity and can be associated with a negative impact [4-7] on quality of life associated with disease severity [8, 9].

Factors potentially related to the development of the PTS are older age, obesity, a history of previous ipsilateral DVT, iliofemoral location of the current thrombosis, failure to promptly recover from the acute symptoms and insufficient quality of oral anticoagulant therapy [10, 11]. Furthermore, it is known that the severity of PTS correlates with the location of the DVT, the more proximal the more severe [3, 12].

The prevalence of iliofemoral thrombosis (IFT) as one major risk factor for developing PTS is not well known in the population. In the recent literature, exact prevalence data concerning IFT are lacking. Previous publications described proximal DVT which may include the common femoral vein with or without the iliac vein. May-Thurner syndrome (MTS) may be one of the major risk factors for the development of left sided IFT, but the prevalence of MTS in IFT patients is still unknown due to difficulties in diagnosing MTS [13].

We have therefore performed a retrospective registry in patients presenting with DVT and IFT to analyze the prevalence of IFT in the overall DVT population. In addition, we performed a prospective registry in a subgroup of patients with IFT who agreed to participate to document

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the severity of PTS, the occurrence of iliac vein compression syndrome in left-sided IFT and quality of life. Additional goals were to identify predictors for the development of severe PTS in this patient population.

Patients and methods

Patients

The CCB vascular center in Frankfurt is the biggest center for vascular diseases in the federal state of Hessen/Germany, where specialists in vascular medicine and vascular surgeons work together in an interdisciplinary team. The patients of our outpatient department are all-comers transferred from general practitioners, oncologists and other disciplines with suspected and finally diagnosed DVT in contrast to patients e.g. seen in University Medical Centers.

We searched the database of our outpatient department for patients who had presented with DVT in the period from 01-Jan-2014 until 30-Jun-2017. Keywords for the database query were: "pelvic vein thrombosis", "iliofemoral thrombosis", "deep vein thrombosis".

847 patients consulted our site in the mentioned period of time with present DVT at time of consultation or past DVT diagnosed after 1996. IFT including the iliac veins was identified in 167 of 847 (19.7%) patients with DVT.

Patients with IFT were asked to be included in the prospective registry, if they fulfilled the following inclusion criteria:

- age between 18 to 80 years
- previously documented IFT by ultrasonography, phlebography, CT or MRI in 1996 or later
- agreement to participate by signing an informed consent.

85 of 167 (50.9%) patients agreed to participate and were included for further analysis (patient screening see Figure 1).

With approval of the responsible ethics committee patient's written informed consent was obtained. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was registered ClinicalTrials.gov ID: NCT03148548.

Methods

In addition to the medical history and clinical examination, the severity of the PTS was quantified using the Villalta-Scale (VS) and the impairment of quality of life (QOL) using the VEINES-QOL/Sym Questionnaire.

Ilio-caval and leg vein duplex-ultrasonography, treadmill ergometry and MR venography were performed under standardized conditions.

Duplex ultrasonography (DUS)

DUS was performed using the Siemens ACUSON X700. The veins were imaged with different transducers and positions based on their location and depth. The ilio-caval veins were examined with a 2 to 4 MHz curvilinear transducer in a lying patient, whereas the deep femoral, popliteal and the infragenual veins were examined using a 4 to 7 MHz linear array transducer while the patient was standing. Post-thrombotic wall-changes and occlusions or the occurrence of May-Thurner syndrome were detected. All patients underwent a DUS.

MR-venography (MRV)

MR-Venography was performed with a 1.5 Tesla Siemens Sonata MRI using the contrast agent Dotarem in a dosage of 0.2 ml/kg bodyweight in order to detect potential existence and extent of postthrombotic changes in the ilio-caval veins, the existence of an iliac vein compression syndrome, hypo- or aplasia of the ilio-caval vein tract in accordance with DUS [14, 15]. MRV was performed in 75

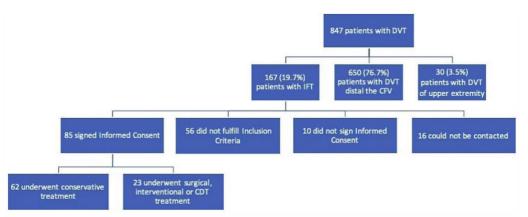


Figure 1. Patient screening. DVT: deep vein thrombosis; IFT: iliofemoral thrombosis; CFV: common femoral vein; CDT: catheter derived thrombolysis.

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patients. 10 patients could not be examined; 3 due to renal insufficiency, 2 due to claustrophobia, 1 due to known allergy against contrast-agents, 4 rejected with no reason.

Definition of May-Thurner syndrome (MTS) and descending IFT

MTS or iliac vein compression syndrome is caused by both mechanical and physiological factors; the chronic pulsatile compression of the left common iliac vein (LCIV) by the crossing right common iliac artery (RCIA) stimulates the formation of fibrotic adhesions that can cause partial or complete iliac vein obstruction over time [15, 16]. To identify MTS DUS (including PW-Doppler) and MRV were used. There is no accurate definition for a hemodynamic relevant MTS in the literature. The anatomical existence of venous compression in the MRV alone does not give information about its hemodynamic relevance [13].

In our registry MTS was defined either when the typical anatomy was detected by the radiologist using MRV and/or by the vascular specialist using DUS.

In our registry only patients with previously documented IFT were included. Furthermore we defined an IFT as "descending", if postthrombotic wall changes were present in the common-iliac vein, the external-iliac vein and the common-femoral veins without postthrombotic changes in the superficial-femoral veins, popliteal veins and infragenual veins evaluated by DUS and MRV. An isolated persistent occlusion of the iliac veins without other postthrombotic wall changes was also defined as a "descending" IFT. An "ascending" IFT was defined, if postthrombotic wall changes were present starting in the infragenual deep veins, popliteal veins and/or femoral veins in addition to the iliac veins.

Treadmill ergometry

Unfortunately, there is no standardized tool for diagnosing venous claudication. Therefore, we used a treadmill-ergometry protocol, which we use to evaluate walking ability in patients with peripheral artery disease [17, 18]. Patients had to walk 250 m with a pitch of 10% and a speed of 3.2 km per hour. Patients were asked, if they had symptoms like cramps, pain or heaviness in their legs. We defined and documented venous claudication (VC), if any of these symptoms occurred during or after the exercise. Both legs were evaluated.

84 patients underwent this examination, 1 patient could not be examined due to disability.

Villalta Score (VS)

The VS is a diagnostic scale for the PTS. It can be used to diagnose and categorize the severity of the condition and is a reliable, valid, acceptable and responsive measure of PTS in patients with previous, objectively confirmed DVT [19]. Five symptoms (pain, cramps, heaviness, paresthesia, pruritus) and six clinical signs (pretibial edema, skin induration, hyperpigmentation, redness, venous ectasia, pain on calf compression) are documented. Points are given for each of these 11 descriptors according to severity,

ranging from 0 for not present to 3 for severe symptoms. Furthermore, if a venous ulcer is present, the severity of the condition is classified as high, regardless of the presence or absence of other signs or symptoms. The patient is diagnosed as having PTS, if the Villalta score is \geq 5 or if a venous ulcer is present. A score of 5–9 defines mild disease, 10–14 moderate disease, and \geq 15 severe disease. We performed the Villalta-score addressing the affected leg in all patients included in the registry.

VEINES-QOL/Sym questionnaire

The VEINES-QOL/Sym is a patient-based questionnaire designed for self-completion (VEINES = Venous Insufficiency Epidemiological and Economic Study). The content and format of questionnaire-items and response scales were modelled after the SF-36 (Short Form) questionnaire, which was developed in the mental health care to evaluate and measure outcome in terms of quality of life and symptom improvement in psychiatric treatment. Generic SF-36 questions were modified to make them specific to venous disease, and new venous-disease-specific questions were developed using the same format and response scales of the SF-36 [20].

The 26-item questionnaire measures the impact of deep venous thrombosis on symptoms (VEINES-Sym scale) and quality of life (VEINES-QOL scale) from the patient's perspective. The items cover symptoms (10 items), limitations in daily activities (9 items), time of day of greatest intensity (1 item), change over the past year (1 item), and psychological impact (5 items). Responses are rated on two-point to seven-point Likert response scales of intensity, frequency or agreement. The time frame for questions about symptoms, daily limitations, and psychological impact covers the previous 4 weeks, as in the SF-36. For both the VEINES-QOL and VEINES-Sym scales, high scores indicate better outcomes. It proved to be a practical, reliable, valid and accessible tool to measure quality of life, outcome and symptoms in adult patients with VTE in the past history [21-23]. Every patient included in the registry had to fill in the questionnaire.

Statistical analysis

Categorical variables are presented as frequencies and percentage and continuous variables as mean \pm standard deviation (SD) or median [min-max] as appropriate. Categorical variables were compared with the Chi-square test or Fisher's exact test and continuous variables with the Wilcoxon-Mann-Whitney-U-Test. A two-sided level of $p \leq 0.05$ was considered as significant. The associations between Villalta scores and BMI, gender or age were evaluated by calculation of bivariate Spearman's correlation coefficient $\rho.$ Confidence intervals for correlations were calculated using a basic bootstrap approach with 1000 replicates. Further univariate and multivariate logistic regression analysis were performed among the variables age, gender, BMI, MTS, DVT and Treatment.

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© 2021 Hogrefe Distributed under the Hogrefe OpenMind License (http://doi.org/10.1026/a000002) Statistical analyses were performed using SPSS software version 26.0 (IBM, Armonk, NY, USA) for Windows.

Results

Prevalence of iliofemoral thrombosis (IFT)

We identified 847 patients presenting with DVT. 35.0% (296/847) patients were diagnosed to have a distal DVT, 41.8% (354/847) patients presented with a proximal DVT excluding the common femoral vein and 19.7% (167/847) patients were identified to have IFT including the iliac veins (see Table I).

Characteristics of patients with IFT included in the prospective registry

50.9% (85/167) of patients with IFT agreed to be included in the registry for further analysis. The index event had occurred on average 4 years (range: 0-20 years) before the time of the investigation.

52.9% (45/85) were female. 76.5% (65/85) had a left-sided IFT, 15.3% (13/85) had a right-sided IFT, and 8.2% (7/85) presented with bilateral IFT. In the majority of patients (69.4%; 59/85) a "descending" IFT was diagnosed.

In 53.8% (35/65) of patients with left-sided IFT, May-Thurner syndrome (MTS) was suspected. "Descending" IFT occurred in 69.2% (45/65) of patients with left-sided IFT and 77.8% (35/45) of these were diagnosed with MTS (see Table II).

27.1% (23/85) of patients with IFT had undergone surgical, interventional or catheter-directed thrombolytic (CDT) therapy while 72.9% (62/85) had received conservative treatment (anticoagulation and compression stockings). Patients in the interventional group were significantly younger (median age 34.0 [16–59] vs. 46.5 [14–76] years, p = 0.021) and presented more often with MTS (77.8% vs. 44.7%, p = 0.025) (see Table II).

Villalta Score (VS)

57.6% (49/85) of the patients had a VS < 5 (no PTS) and 31.8% (27/85) had a VS of 5-9 (mild PTS). Moderate or severe PTS (VS \geq 10) was observed in 10.6% (9/85) of the patients (see Figure 2). No patient had an active or healed venous ulcer, neither in medical history, nor when presenting in the outpatient clinic. No significant differences between conservatively and interventionally treated patients were observed.

The VS did not differ between men and women. No significant difference of the VS was observed comparing the ascending IFT-group with the descending IFT-group (VS: median 4 [0-12] vs. VS: median 3 [0-22], p = 0.578) and comparing the IFT-group with no MTS with the IFT-group

Table I. Prevalence of different types of deep vein thrombosis (screening period: 2014–2017)

	Patients with DVT
Type of DVT	n = 847 (%)
Distal DVT; n (%)	296 (35.0)
Femoro-popliteal DVT; n (%)	354 (41.8)
Iliofemoral DVT; n (%)	167 (19.7)
DVT of upper limb; n (%)	30 (3.5)

DVT: Deep Vein Thrombosis; Distal DVT: DVT of one or more infragenual or muscle veins; Femoro-popliteal DVT: DVT of infragenual, popliteal and femoral veins; Iliofemoral DVT: Femoro-popliteal DVT including the iliac vein thrombosis

with MTS (no MTS VS: 4 [0-22], MTS VS: 3 [0-19], p = 0.868).

Analysing the severity of the PTS in dependence of the time after the event we did not observe a relevant increase of the VS during a period of 20 years regardless of the type of therapy (conservative or interventional treatment) (see Figure 3).

Venous claudication

The prevalence of venous claudication in the overall study population was 10.6% (9/85) and was numerically slightly different between the conservative and the interventional group (9.7% vs. 13.0%; p = 0.698). Patients with moderate or severe PTS (VS \geq 10) presented more often with venous claudication compared to patients with no or mild PTS (VS < 10) (22.2% (2/9) vs. 9.2% (7/76), p = 0.242).

Quality of life

Quality of Life in the overall study population was high (combined VEINES-QOL/Sym-Score: median 86 [38–103]). Comparison of the VEINES Scores revealed no significant difference between the conservative and the interventional treatment group (combined VEINES-QOL/Sym-Score: median 88 [38–103] versus 83 [51–103]; p=0.839) (see Table III). A high negative correlation between the VEINES Score and the severity of the PTS was observed (ρ (CI 95%) = -0.63 (-0.76; -0.46); p < 0.01) (see Figure 4).

Predictors for PTS and venous claudication

Using the univariate logistic regression analysis a high BMI was identified as a significant predictor for developing a moderate or severe PTS (VS \geq 10). Other variables as age, gender, existence of May-Thurner syndrome, type of DVT (ascending or descending) or the type of therapy (conservative or interventional) were not independent predictors for clinically relevant PTS. To verify this result a multivariate logistic regression analysis was performed in

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Table II. Baseline characteristics of patients with IFT who agreed to participate in the prospective registry

	All	Conservative therapy	Interventional therapy	
	n = 85	n = 62	n = 23	p-value
Age; median [min-max]	40.0 [15-76]	46.5 [15-76]	34.0 [16-59]	0.021
Female; n (%)	45 (52.9)	32 (51.6)	13 (56.5)	0.808
BMI; median [min-max]	27 [19-46]	27 [19-46]	25 [20-44]	0.414
BMI 18.5-24.9; n (%)	27 (31.8)	17 (27.4)	10 (43.5)	0.269
BMI 25-29.9; n (%)	37 (43.5)	30 (48.4)	7 (30.4)	
BMI ≥ 30; n (%)	21 (24.7)	15 (24.2)	6 (26.1)	
Period of time (years) between occurrence of IFT and examination; median [min-max]	4 [0-20]	3 [0–20]	5 [1–17]	0.363
IFT right-sided; n (%)	13 (15.3)	12 (19.4)	1 (4.4)	0.058
IFT both-sided; n (%)	7 (8.2)	3 (4.8)	4 (17.4)	
IFT left-sided; n (%)	65 (76.5)	47 (75.8)	18 (78.3)	
IFT left-sided with MTS; n (%)	35 (53.8)*	21 (44.7)*	14 (77.8)*	0.025
"Ascending" IFT; n (%)	26 (30.6)	21 (33.9)	5 (21.7)	0.427
"Descending" IFT; n (%)	59 (69.4)	41 (66.1)	18 (78.3)	

BMI: body-mass-index; IFT: iliofemoral thrombosis; DVT: deep vein thrombosis; MTS: May-Thurner syndrome. *Based on patients with left-sided IFT.

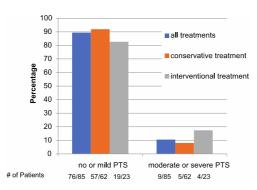


Figure 2. Occurrence of postthrombotic syndrome defined by the Villalta Score PTS: postthrombotic syndrome; No or mild PTS: Villalta Score < 10; moderate or severe PTS: Villalta Score \geq 10.

addition. Again BMI was the only significant predictor for a moderate or severe PTS (VS \geq 10) (see Table IV).

Similar results were observed when analyzing predictors for venous claudication: a high BMI was a significant predictor for the development of venous claudication (OR 1.155 [95% CI: 1.029-1.295]; p=0.014).

Discussion

Although the most common location of DVT is a femoropopliteal or distal thrombosis, iliofemoral thrombosis was diagnosed in nearly 20% of the examined population with DVT. Additionally, in the majority of patients the IFT was located on the left side. Left sided "descending" IFT was associated with MTS, which suggests that MTS might be one of the major risk factors for the development of this

type of IFT. Although many uncertainties exist regarding the prevalence of MTS and its pervasiveness in DVT [13] our registry provides for the first time a systematic analysis of the possible relationship between left sided "descending" IFT and MTS as a possible reason.

Reported prevalences of PTS after DVT differ widely among studies because of differences in study populations, tools used to assess PTS and time interval between acute DVT and PTS assessment. Up to 10% will develop severe PTS [24]. So far it has been assumed that the risk of developing moderate or severe PTS is increased in patients with IFT compared to patients with proximal lower limb DVT excluding the iliac veins or compared to infrapopliteal DVT [24].

In our registry, the majority of patients with IFT had no or mild PTS and moderate or severe PTS was observed in every tenth patient while none of them had developed a venous ulcer at any time. In the recently published prospective CACTUS-PTS-study the long-term risk to develop moderate or severe postthrombotic syndrome after symptomatic distal deep vein thrombosis (VS \geq 10) was 7% after 6 years of follow up [25] and was therefore not much different to our findings although focusing on distal DVT.

Ende-Verhaar analyzed the short and long-term incidence of PTS in patients included in the MEGA-study. No differentiation between proximal DVT including the iliac veins and distal DVT was performed. After one year the incidence of severe PTS (VS \geq 7) was 5.6% for all types of DVT which decreased to 2.1% after 8 years [26]. They could show that the symptoms of PTS improved many years after the index event in a large proportion of cases. This may be an explanation for our findings that the severity of PTS did not change over time.

As one can expect it could be demonstrated in our registry that the grade of PTS had a significantly high negative

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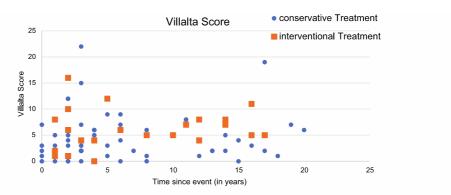


Figure 3. Scatter Plot of the Villalta Score depending on the period of time (years) after the occurrence of IFT (n = 85), (ρ (Cl 95%) for conservative Treatment = 0.15 (-0.09; 0.39), ρ = 0.232; ρ (Cl 95%) for interventional Treatment = 0.26 (-0.19; 0.66), ρ = 0.224).

Table III. Results of the Quality of Life - VEINES Scores (higher score indicates better outcome), Wilcoxon-Mann-Whitney-U-Test

VEINES-Scores	All n = 85	Conservative n = 62	Interventional n = 23	p-value
Clinical Symptoms (VEINES-Sym score) median [min-max]	41 [14-48]	40.5 [14-48]	41 [20–46]	0.448
Quality of life (VEINES-QOL score), median [min-max]	46 [24-57]	46.5 [24-57]	45 [24-57]	0.452
Combined VEINES-QOL/Sym score median [min-max]	86 [38–103]	88 [38–103]	83 [51–103]	0.839

Table IV. Uni- and multivariate analysis of risk factors for moderate or severe PTS (Villalta Score ≥ 10)

	Univariate		Multivariate		
Variable	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value	
Age	1.018 (0.982-1.055)	0.341	1.059 (0.991-1.131)	0.088	
Gender					
Male	0.527 (0.123-2.263)	0.389	0.370 (0.047-2.877)	0.342	
female	Reference				
BMI	1.182 (1.048-1.333)	0.007	1.237 (1.035-1.477)	0.019	
MTS					
Yes	3.241 (0.752-13.973)	0.115	7.984 (0.469-135.959)	0.151	
No	Reference				
IFT					
Ascending	0.619 (0.120-3.205)	0.568	1.495 (0.079-28.159)	0.788	
Descending	Reference				
Treatment					
Conservative	0.417 (0.101-1.713)	0.225	0.181 (0.021-1.582)	0.122	
Interventional	Reference				

BMI: Body-Mass Index; MTS: May-Thurner syndrome; IFT: Iliofemoral Thrombosis.

impact on the quality of life. Therefore avoidance of severe PTS is one of the major goals to increase quality of life after occurrence of IFT in this patient population.

In our prospective registry nearly every third patient received interventional treatment. These patients were younger on average and presented mainly with left sided IFT and MTS. The incidence of PTS of the interventionally treated patients was comparable to the conservatively treated patients.

In prospective randomized trials conflicting outcomes concerning the prevention of postthrombotic syndrome have been published when comparing additional catheter-directed thrombolysis (CDT) to standard therapy (ST) [27-29]:

In the CAVA-trial the incidence of PTS was analyzed in patients with complete or partial thrombosis of the common femoral vein or more cranial vein segments after 12 months [28]. No significant difference of PTS was observed in the two groups (29% in the CDT group vs. 35% in ST group (OR 0.75 [95% CI 0.38–1.50]; p = 0.42).

In the ATTRACT-trial the incidence of PTS was determined in patients with femoral, common femoral, or iliac vein thrombosis after 6 and 24 months [29]. Again PTS was not significantly different between the interventional

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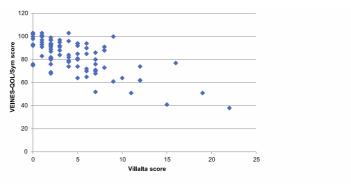


Figure 4. Correlation Analysis between quality of life (combined VEINES-QOL/Sym Score, higher score indicates better outcome) and postthrombotic syndrome (Villalta Score) (ρ (Cl 95%) = -0.63 (-0.76; -0.46), p < 0.01).

group compared to the standard group (47% vs. 48%; OR 0.96 [95% CI 0.82-1.11]; p = 0.56 after 24 months).

In the CaVenT-trial the incidence of PTS in patients with a DVT above mid-thigh level was analyzed after 24 months [27]. A significantly lower incidence of PTS was observed in the interventional group compared to the standard treatment group (41.1% vs. 55.6%; OR 0.75 [95% CI 0.2–27.9]; p = 0.047). In contrast to these trials the involvement of the iliac veins was the main criteria for inclusion in our prospective registry.

We could identify a high BMI as the major independent predictor for the development of a moderate to severe PTS and of venous claudication in IFT patients which is in accordance with the current literature [30, 31]. Rabinovich et al. described a doubling of the risk of developing PTS (OR 2.17, p=0.008), when the BMI was $\geq 35~{\rm kg/m^2}$ [30]. Rattazzi et al. could show that patients with PTS presented with a significantly higher BMI than DVT-patients without PTS (p = 0.005) [32]. Obesity (BMI $> 30~{\rm kg/m^2})$ more than doubles the risk of PTS and weight loss may be a useful measure to reduce the risk of developing PTS, although not yet proven in literature [24].

Limitations

There are some limitations of the registry: Patients presenting with an IFT were not randomized neither to the conservatively nor to the interventionally treated cohort. It could well be that only severely affected patients were treated interventionally while patients with milder symptoms received conservative treatment only. In addition, the two examined cohorts in our registry are not big enough to observe significant differences between different treatment options. In addition, the interventionally treated group was very heterogenous and included patients who had received thrombectomy and AV-fistula, percutaneous interventions with or without stenting and/or catheter-directed thrombolysis.

The type and duration of the anticoagulant therapy after diagnosis of DVT could not be documented partly due to

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poor patients' memory and the retrospective design of data documentation at inclusion.

Conclusions

IFT is frequently observed in DVT. None of the patients with IFT presented with a venous ulcer, 10% developed moderate or severe PTS and 10% presented with venous claudication.

One could cautiously conclude that with conservative therapy the results with regard to the occurrence of a postthrombotic syndrome may not be all that bad and possibly only a few patients might benefit from revascularization. One could further discuss that based on our data it could probably be more beneficial to wait a certain time before revascularization in the case of fresh descending thrombosis, whether the conservative therapy is effective and only to revascularize the minority of patients who after 6 Months are still severely symptomatic.

Prospective trials with randomization for interventional or conservative treatment in case of acute IFT explicitly including the iliac veins are needed. These results will help to decide whether acute interventions can improve the outcome of PTS in this patient population.

Since the majority of patients with conservatively treated IFT present with no or mild symptoms of PTS, patients with moderate to severe PTS and/or venous claudication might profit most from modern interventional strategies.

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History

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Conflicts of interests

No conflicts of interest exist.

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Darstellung des eigenen Anteils an der Publikation

Konzeption der Fragestellung und Zielsetzung in Zusammenarbeit mit Frau Prof. Dr. Lindhoff-Last. Patientenrecherche und -selektion sowie Definition der Einund Ausschlußkriterien.

Konzeption und Erstellung des Patientenanschreibens, der Einverständniserklärung (informed consent) und des Patienten-Anamnesebogens. Auswahl und Zusammenstellung der Untersuchungen, die die Patienten erhalten sollten.

Antragstellung und Einholung des Ethikvotums bei der Ethikkommission der Landesärztekammer Hessen.

Datensammlung, anschließend Erstellung der Statistik in Zusammenarbeit mit Fr. U. Balaban (Institut für Biostatistik und Mathematische Modellierung, Universitätsklinikum Frankfurt), Auswertung und Interpretation der Ergebnisse in Zusammenarbeit mit Frau Prof. Dr. Lindhoff-Last, Erstellung der Tabellen und Graphiken der Publikation (Korrekturen durch Frau Prof. Dr. Lindhoff-Last und Herr Prof. Dr. Schellong). Im Weiteren Verfassung der wissenschaftlichen Publikation (Korrekturen durch Frau Prof. Dr. Lindhoff-Last). Schließlich Verfassung der publikationsbasierten Dissertation.

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Lebenslauf 1/3

Lebenslauf 2/3

Lebenslauf 3/3

Schriftliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die dem Fachbereich Medizin der Johann-Wolfgang-Goethe-Universität Frankfurt am Main zur Promotionsprüfung eingereichte Dissertation mit dem Titel

Incidence and severity of postthrombotic syndrome after iliofemoral thrombosis - Results of the Iliaca-PTS - Registry

im CardioAngiologischen Centrum Bethanien, Frankfurt am Main unter Betreuung und Anleitung von Prof. Dr. Edelgard Lindhoff-Last mit Unterstützung durch Dr. Johannes Renczes und Prof. Dr. Sebastian Schellong ohne sonstige Hilfe selbst durchgeführt und bei der Abfassung der Arbeit keine anderen als die in der Dissertation angeführten Hilfsmittel benutzt habe. Darüber hinaus versichere ich, nicht die Hilfe einer kommerziellen Promotionsvermittlung in Anspruch genommen zu haben.

Ich habe bisher an keiner in- oder ausländischen Universität ein Gesuch um Zulassung zur Promotion eingereicht. Die vorliegende Arbeit wurde bisher nicht als Dissertation eingereicht.

Vorliegende Ergebnisse der Arbeit wurden in folgendem Publikationsorgan veröffentlicht:

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