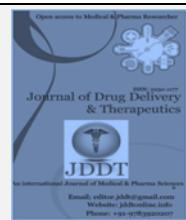


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Research Paper

## Epidemioclinical profile and management of post thrombotic syndrome in Antananarivo

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### Abstract

**Introduction:** The post-thrombotic syndrome (PTS) is the most complication of deep vein thrombosis who deserves an early management. The aim of this study was to determine the epidemioclinical profile and the management of PTS.

**Methods:** This was a retrospective and descriptive study for a period of 6 years from January 2013 to December 2018, performed at the Cardiovascular Surgery Unit in JRA Teaching Hospital Antananarivo, including all patients who presented post-thrombotic syndrome after an acute episode of deep venous thrombosis.

**Results:** 106 patients were recorded among 315 patients who presented an episode of DVT (33.65%) and 14110 patients admitted in this period (0.75%). The average age was 46.18 years old. There were 30 males (28.30%) and 76 female (71.69%). The most important risk factors of PTS were previous history of varicose veins (50%), sedentary lifestyle (45.28%), insufficiency of anticoagulant therapy (68.86%) and proximal DVT (47.16%). Delayed of diagnosis were greater than or equal to 2 years after an acute DVT in 86 patients (81.13%). The most clinical signs were edema (56.60%) and varicose veins (54.71%). According the Villalta's score, PTS were mild in 48 patients (45.28%), moderate in 47 patients (44.33%) and severe in 11 patients (10.37%). Management was lifestyles change (45.28%), compression stockings (100%), anticoagulant therapy (100%) and surgical treatment (65.09%).

**Conclusion:** The frequency of PTS was 33.65% in our study. PTS reduces quality of life of patients, but it can be avoided if the treatments of DVT are adapted.

**Keywords:** Deep vein thrombosis, Post-thrombotic syndrome, Epidemiology, Management

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### INTRODUCTION

Postthrombotic syndrome is defined as a presence of symptomatology and or chronic venous signs after deep vein thrombosis in the lower limbs.<sup>1</sup> PTS is the most frequent complication of DVT, which develops in 20 to 50% of cases after proximal DVT and is severe in 5-10% of cases.<sup>2</sup> According the literature, the cumulative incidence of PTS for 2 years after an acute episode of DVT is 23-60%, but the cumulative incidence of severe PTS for 5 years is 1-30%.<sup>3</sup> PTS has been increasingly recognized as a serious public health problem. Because of venous ulcer, the patient's quality of life is seriously affected because of obstacles to daily routine activities and increased cost of treatment. According to Ma's study in 2014, the mean total cost of treating venous

leg ulcers in contemporary vascular practice was \$15,732.<sup>4</sup> One major issue in early PTS research concerned the risk factors and the management of PTS. PTS is little-known, underappreciated by practitioner in Madagascar and there is no consensus among their management. The aim of this study was to describe the epidemioclinical profile and management of PTS in our department.

### METHODS

We conducted a retrospective and descriptive study for a period of 6 years from January 2013 to December 2018, performed at the Cardiovascular Surgery Unit in JRA Teaching Hospital Antananarivo, including all patients who presented postthrombotic syndrome after an acute episode DVT.

### Inclusion criteria

All patients who had a previous history of acute DVT and presenting symptoms or clinical signs of chronic venous insufficiency (greater than or equal to 3 month after an acute episode of DVT) were included in this study.

### Exclusion criteria

Patients presented a symptomatology or clinical signs of chronic venous insufficiency but not having a previous history of DVT had been excluded.

Data were collected from patients folders stored at the Cardiovascular Surgery Unit in Joseph Ravoahangy Andrianavalona (JRA) Teaching Hospital Antananarivo.

Demographic data, risk factors of PTS, delay of diagnosis after initial DVT, symptoms and clinical signs, Villalta score, results of duplex ultrasound and management. Statistical analysis was performed by use of the SPSS® 21 statistics software program.

## RESULTS

One hundred and six patients were recorded among 315 patients who presented a previous history of DVT (37.73%) and 14110 patients admitted during this period (0.75%). The average age was 46.18 years old (from 19 to 88 years old) and 8.49% of patients was older than 60 years. Patients were 30 males (28.30%) and 76 females (71.69%), giving a sex ratio of 0.39 (Table I).

**Table I : Characteristics of study participants.**

Characteristics	No. of Patients (Total=106)		Percentage (%)
<b>Gender</b>	Male	30	28.30
	Female	76	71.69
<b>Age category (years)</b>	0-30	11	10.37
	31-40	25	23.58
	41-50	44	41.50
	51-60	17	16.03
	61-70	04	03.77
	≥ 71	05	04.71

The most important risk factors of PTS were previous history of varicose veins (50%), sedentary lifestyle (45.28%), insufficiency anticoagulation therapy (68.86%) and proximal DVT (47.16%) (Table II). Delayed diagnosis of PTS after an acute DVT were greater than or equal to 2 years in 86 patients (81.13%) and less than 2 years in 20 patients

(18.86%). Symptoms were pain (42.45%), cramps (28.30%), heaviness (51.88%), pruritus (18.86%) and paresthesia (20.75%). The most clinical signs were edema (56.60%) and varicose veins (54.71%). According the Villalta's score, PTS were mild in 48 patients (45.28%), moderate in 47 patients (44.33%) and severe in 11 patients (10.37%) (Table II).

**Table II : Risk factors of PTS and diagnosis**

	Risk factors and diagnosis	No. of Patients (Total=106)	Percentage (%)
<b>Risk factors</b>	Advanced age (≥ 60 years)	09	08.49
	Obesity (BMI≥30kg/m <sup>2</sup> )	25	23.58
	Previous history of reccurent DVT	35	33.01
	Previous history of varicose veins	53	50.00
	Sedentary lifestyle	48	45.28
	Insufficiency anticoagulation therapy	73	68.86
<b>Delay of diagnosis after initial DVT</b>	Proximal DVT	50	47.16
	< 2 years	20	18.86
<b>Symptoms</b>	≥ 2 years	86	81.13
	Pain	45	42.45
	Cramps	30	28.30
	Heaviness	55	51.88
	Pruritus	20	18.86
<b>Clinical signs</b>	Paresthesia	22	20.75
	Telangiectasia	35	33.01
	Varicose veins	58	54.71
	Edema	60	56.60
	Hyperpigmentation	22	20.75
	White scar tissue	20	18.86
	Lipodermatosclerosis	15	14.15
<b>Villalta's PTS score</b>	Venous ulcer	11	10.37
	Mild (5-9)	48	45.28
	Moderate (10-14)	47	44.33
	Severe (≥15 or presence of ulcer)	11	10.37



**Figure 1:** Bilateral venous ulcer in patient treated in JRA Hospital

DVT were proximal in 50 patients (47.16%), located in iliofemoral vein in 20 patients (18.86%) and in popliteal vein in 30 patients (28.30%) (Table III). DVT were located in left side in 65 patients (61.32%), in the right side in 39

patients (36.79%) and bilateral in 2 patients (1.88%). Duplex ultrasound showed venous abnormalities in 90 cases (84.90%).

**Table III : Duplex ultrasound results**

Duplex ultrasound result	No. of Patients (Total=106)	Percentage (%)
Location of initial DVT	Ilio-femoral vein	20
	Popliteal vein	30
	Tibial vein	56
Side of the DVT	Left	65
	Right	39
	Bilateral	02
PTS venous abnormalities	Distended veins	58
	Non-compressible	53
	Reflux	53
	Limited lumen stenosis	45
	Normal	16

Management was non-interventional treatment and surgical treatment: non interventional-treatment were lifestyle changes in 48 patients (obese or overweight) (45.28%), compression stockings for all patients (100%) and anticoagulant therapy for all patients (100%) (Table IV).

Surgical treatment were stripping in 34 patients (32.07%), phlebectomy in 5 patients (04.71%), stripping in association with phlebectomy in 30 patients (28.30%). Local treatment has been performed in 11 patients (10.37%) who presented venous ulcers.

Table IV : Treatment of post thrombotic syndrome

Treatment		No. of Patients (Total=106)	Percentage (%)
Non-interventional treatment	Lifestyle changes	48	45.28
	Compression stockings	106	100
	Anticoagulant therapy	106	100
	• < 3months	106	54.71
	• 3-6 months	80	75.47
	• 6-12 months	51	48.11
	• > 12 months	26	15.09
Surgical treatment (n=69)	Stripping	34	32.07
	Phlebectomy	05	04.71
	Stripping + phlebectomy	30	28.30
	Local treatment of ulcer	11	10.37

## DISCUSSION

PTS is the most complications of DVT in patients with lower extremity deep venous thrombosis, including all symptoms and clinical signs after an episode of acute DVT. The pathophysiology of post thrombotic syndrome is unclear. However, some authors elucidated the pathophysiology of PTS, determining the role of chronic venous obstruction, venous insufficiency, increased exposure to inflammatory mediators and reduced mobility in patients who have DVT.<sup>5, 6</sup>

The frequency of PTS after a first episode of acute symptomatic DVT of lower extremity were variable according the study: 13% in Nishimoto's study, 11% in Ondze-Kafata's study and 12% in Saleh's study.<sup>7,8,9</sup> In our study, the frequency of PTS was higher than in these results (33.65%). However, the frequency of PTS in our study was less than in Huang's study (47.7%).<sup>10</sup>

Older age (greater than or equal to 60 years) is one of factors increased the risk of PTS after DVT.<sup>11</sup> In our study, 8.49% of patients was older than 60 years. The predominance of older age of patients are seen in several study but the average age varied according the study: 47 years in the one of Kahn's study, 50 years in Delluc's study, 63 years in Mant's study and 46 years in our study.<sup>12,13,14</sup>

Women were a significantly greater risk for PTS showed by some researchers.<sup>15,16</sup> The predominance of female is still observed in several study of PTS as in Tick's study (53%), in Huang's study (53%) and in our study (71%).<sup>15,10</sup> This predominance of female could be explained by the presence of a significant risk of DVT in female than male ( $p=0.003$ ).<sup>17</sup>

In the literature, the relative importance of risk factors of PTS has been subject to considerable debate. According Kahn's study, the principal risk factors for PTS are anatomically extensive DVT, recurrent ipsilateral DVT, persistent leg symptoms 1 month after acute DVT, obesity, and older age.<sup>11</sup> According to Tick's study, women, obese patients, patients with proximal DVT and those with varicose veins have an increased risk of PTS.<sup>15</sup> However, other recent study showed the significant risk factors of PTS as in Nishimoto's study, in Huang's study and in Zhang's study.<sup>7,10,18</sup> In our study, the most risk factors of PTS were obesity (33.73%), previous history of varicose veins (50%),

sedentary lifestyle (45.28%), insufficiency anticoagulation therapy (68.86%) and proximal DVT (47.16%).

PTS develops in ~20% to 50% of patients within 2 years of DVT diagnosis.<sup>19</sup> In our study, 81% of patients presented PTS greater than or equal to 2 years after an acute episode of DVT. The diagnosis of PTS is most difficult established. In Schulman's study, any sign of PTS was seen in 56.3% of the evaluated patients.<sup>20</sup> According to the consensus of International Society on Thrombosis and Haemostasis (ISTH) in 2008, Villalta's score constitute the gold standard to establish the diagnosis of PTS. Villalta's score is based on 5 symptom (pain, cramps, heaviness, paresthesia, pruritus) and six clinical signs (pretibial edema, skin indurations, hyperpigmentation, redness, venous ectasia, pain on calf compression).<sup>21</sup> Points are given for each of these 11 descriptors according to severity, ranging from 0 for not present to 3 for severe. The patient was diagnosed as having PTS if the Villalta score was  $\geq 5$  or if a venous ulcer was present. A score of 5-9 signifies mild disease, 10-14 moderate disease and  $\geq 15$  or development of venous ulcer signifies severe disease. In our study, PTS was mild in 48 patients (45.28%), moderate in 47 patients (44.33%) and severe in 11 patients (10.37%).

In the literature, mild forms is usually frequent than severe forms. According to Kahn's study, PTS were mild in 30%, moderate in 10% and severe in 3% of patients.<sup>16</sup> According the retrospective study of PTS in 11 children by Sharathkumar et al, PTS were moderate in 72% of patients and severe in 28% of patients.<sup>22</sup> In Bigguzzi's study, PTS were mild in 55%, moderate in 4% and severe in 4% of patients.<sup>23</sup> Our study agrees with most studies in the literature in the predominance of mild form than severe form. According Schulman's study, the probability to develop severe PTS was 6%.<sup>20</sup>

Duplex ultrasound can provide additional information on location of initial DVT, extension of thrombosis. The advantage of duplex US is that the exam is inexpensive and non-invasive. In our study, DVT were located in proximal veins in 47.16% of patients which 18.86% in iliofemoral veins and 28.30% in popliteal veins. According to Bittar's study, DVT were located in proximal vein in 90.3% of cases and in distal vein in 9.7% of cases.<sup>24</sup> In Huang's study, DVT

were proximal in 82.2%.<sup>10</sup> According to the literature, proximal DVT is a significant risk factor of PTS.<sup>15,25</sup> The predominance of left side of DVT were observed in most studies as in Rabinovich's study, in Huang's study.<sup>26,10</sup> According to Rabinovich study, DVT were located in left side in 55.4% of patients and in right side in 44.6%.<sup>26</sup> According to Huang study, DVT were located in left side in 65.4% and in right side in 34.6%.<sup>10</sup> Our results were similar to these study in the predominance of left side (61.32%). This predominance of left side in DVT's location was due to the left-sided iliac vein compression syndrome, also known as May-Thurner syndrome, which explains the starting point of DVT from this location.<sup>27,28</sup> However, Avila's study in children PTS showed the predominance of right side (50%) than left side (43%).<sup>29</sup> Duplex ultrasound could analyzed the anatomy and hemodynamic profile of lower-limb veins. For post thrombotic syndrome, duplex ultrasound can recognize specific anatomical abnormalities in the venous lumen, wall, and valves.<sup>30</sup> In our study, venous abnormalities were encountered in 84.90% of results of duplex ultrasound.

If the duplex US is inconclusive or additional anatomical information is required, CT or MR venography can be performed to evaluate for venous collaterals, masses that may cause extrinsic compression of veins, and venous asymmetries.

Currently debate continues about the best strategies for the management of PTS. There is no consensus about management of PTS. However, Kahn and al has established guidance for the prevention and treatment of PTS in 2016.<sup>31</sup> Otherwise, some researchers has elucidated in recent studies the prevention and management of PTS as in Makedonov's study in 2020, in Rabinovich's study in 2018, in Ten CateHoek's study in 2018 and in Azirar's study.<sup>32,33,34,35</sup> Now, there are some therapeutic possibilities to treat PTS after an episode of DVT: lifestyle change, compression stockings, pharmacotherapy and surgical treatment.<sup>36</sup> These therapeutic possibilities could be used isolated or in combination. In our study, the therapeutic modalities were 45% lifestyle changes, 100% compression stockings, 69% pharmacotherapy and 65% surgical treatment. The efficacy of compression stockings to prevent PTS in patients with DVT has been demonstrated in Burgstaller's study.<sup>37</sup> The results of two randomized controlled trials (RCTs) in Burgstaller's study showed a statistically significant reduction in PTS of 50% or more after two or more years of using active compression stockings.<sup>37</sup> Anticoagulation insufficiency is one of risk factors for developing PTS. So, the use of anticoagulant medication such as direct oral anticoagulants (DOACs) might decrease PTS incidence in patients presenting DVT.<sup>34</sup> Recurrent ipsilateral DVT is an important risk factor for PTS so preventing recurrent DVT by providing optimal, appropriate-duration anticoagulation for the initial DVT is an important goal of management. In our study, all patients received an anticoagulation treatment by vitamin K antagonist but 48.11% of patients received anticoagulant therapy during greater than or equal to 6 months. It could be explained by the cost of treatment which many patients could not follow for a long time. However, Shulman and al. analogously showed in a 10 year follow-up study of the Duration of Anticoagulation (DURAC) trial that the risk of PTS was not significantly different between the 6 weeks and 6 months arms.<sup>38</sup>

Surgery or endovascular therapy should be considered as complementary to medical management. Early surgical or endovascular intervention in appropriately selected patients may decrease the incidence of recurrent ulceration and skin

changes and provide a better quality of life. Khanna and al have described the surgical possibilities to treat PTS in 2012.<sup>39</sup> Venous obstruction requires endovenous stenting, endophlebectomy, or open bypass procedures. Venous stripping, foam sclerotherapy, radiofrequency, or laser ablation are used to abolish superficial venous reflux. Valvuloplasty procedures are useful for incompetent valve but in intact deep venous valves, while transposition vein or axillary vein autotransplantation is done for completely destroyed valves. In our study, surgical treatment was stripping (32.07%), phlebectomy (4.71%) and stripping in association with phlebectomy in 30 patients (28.30%). The treatment of chronic venous ulcers is a therapeutic challenge. Rai concluded that patients with nonhealing venous ulcers who have had compression therapy and have no deep vein incompetence are recommended for superficial venous surgery, foam sclerotherapy or ligation of the affected vein as an important aspect of the overall treatment plan.<sup>40</sup> Prevention of recurrences includes regular clinical evaluations, patient education about skin care, elevation, exercise and life-long compression therapy. In our practice, the treatment of venous ulcer includes local treatment (debridement, dressings, and skin graft), compression stockings and stripping.

## CONCLUSION

PTS increases healthcare costs and reduces quality of life of patients. The frequency of PTS after an acute episode of DVT was 33.65% in our study. DVT required an early management to prevent PTS. Venous ulcer is the most serious clinical signs which treatment requires control of the high pressure in the leg veins and treating the ulcer.

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## Conflicts of Interest:

The authors have no conflicts of interest to declare.

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