



Treatment-Related Outcomes in Paget–Schroetter Syndrome— A Cross-Sectional Investigation

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Objective To investigate treatment-related outcomes, namely radiological clot resolution, post-thrombotic syndrome (PTS), and health related quality-of-life (HRQoL) scores, in children with Paget–Schroetter syndrome (PSS) undergoing multidisciplinary management, including anticoagulation and decompressive rib-resection surgery, with or without thrombolytic therapy.

Study design We identified all patients treated for PSS at our institution between the years 2010 and 2017. Baseline clinical and radiologic data were abstracted from medical records. Two validated survey instruments to quantify PTS and HRQoL were mailed to eligible patients. Standard statistical methods were used to summarize these measures.

Results In total, 22 eligible patients were identified; 10 were treated with thrombolysis followed by anticoagulation and rib resection, and 12 were treated with anticoagulation and rib resection alone. Nineteen patients responded to the survey instruments. Median age at deep vein thrombosis diagnosis and survey completion were 16.3 and 20.4 years, respectively. Nineteen of 22 patients had thrombus resolution on radiologic follow-up. Fourteen of 19 survey respondents reported signs/symptoms of PTS of which the majority (12/14) reported mild PTS. Aggregate total, physical, and psychosocial HRQoL scores reported were 90.6, 96.7, and 93.3, respectively. Thrombolytic therapy was not associated with a significant improvement in radiologic, clinical or HRQoL outcomes.

Conclusions Most patients with PSS had complete thrombus resolution on imaging. Only 11% of survey respondents reported moderate PTS. The entire cohort reported excellent HRQoL scores. The role for thrombolytic therapy in the management of childhood PSS remains incompletely elucidated. (*J Pediatr* 2019;207:226-32).

Paget–Schroetter syndrome (PSS), also known as venous thoracic outlet syndrome, occurs secondary to the extrinsic compression and impingement of the subclavian vein as it passes through the thoracic outlet, eventually resulting in upper extremity deep venous thrombosis (DVT).¹⁻⁴ The compression may occur secondary to hypertrophy of the scalene, subclavius, or pectoralis minor muscles or anatomic abnormalities such as a cervical rib or aberrant insertion of the costoclavicular ligament.⁵ This condition typically affects the dominant arm of healthy and athletic young adults, who often give a history of repeated overhead activities. Management of PSS in adults involves a combination of anticoagulation, thrombolysis, angioplasty, and decompressive surgery.⁶

In contrast to the extensive adult literature, PSS has only been recently described in children, and the optimum management strategy is unclear.⁷ In 2006, Brandao et al described 6 children with PSS who were treated with anticoagulation for 6 months.⁸ Treatment was complicated by nonresolution of symptoms, recurrent thrombosis, and moderate-to-severe post-thrombotic syndrome (PTS). In 2009, Rigberg et al also described 6 children with PSS who were treated with thrombolysis, decompressive surgery and 3 months of anticoagulation.⁹ At last follow-up, all patients were free of symptoms and were able to resume their competitive athletic activities. The relevance of decompressive surgery has since been highlighted in other pediatric cohorts.^{5,10,11} However, none of the published pediatric studies have used standardized measures to document the presence and severity of PTS or health related quality-of-life (HRQoL). In addition, the need for upfront thrombolytic therapy in children remains unclear and has been debated recently in adult PSS cohorts.^{12,13}

The management of PSS at Nationwide Children's Hospital (NCH) has evolved over the last decade. Through 2013, all patients were treated with anticoagulation and decompressive rib-resection surgery, with thrombolytic therapy being

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DVT	Deep venous thrombosis
HRQoL	Health-related quality of life
NCH	Nationwide Children's Hospital
PSS	Paget–Schroetter syndrome
PTS	Post-thrombotic syndrome

reserved for patients with severe symptoms at presentation. After 2013, all patients have been treated with upfront pharmacomechanical and/or catheter-directed thrombolysis followed by anticoagulation and decompressive rib-resection surgery. The purpose of this study was to document the clinical, radiologic, and HRQoL outcomes in patients with PSS managed at our institution. We also sought to compare outcomes between patients who received upfront thrombolytic therapy and those who did not.

Methods

Permission for this study was obtained from the institutional review board. The electronic data warehouse at NCH was searched using *International Classification of Diseases, Ninth Revision, Clinical Modification* codes to identify all cases of upper extremity thrombosis diagnosed over an 8-year period (January 1, 2010, to December 31, 2017). Medical records of these patients were then reviewed to identify eligible subjects, defined as children, aged 0-21 years with noncatheter-related, effort-induced thrombosis of the axillary and/or subclavian vein. To be eligible, patients had to have a history of repetitive overhead activities and/or documentation of extrinsic compression

of the subclavian vein on dynamic venous imaging (**Figure 1**) per criteria established by the Society for Vascular Surgery.¹⁴ Patients who did not receive upfront therapy at NCH but were referred for a second opinion/decompressive surgery alone were excluded from further analysis. Baseline demographic data abstracted from the medical records of eligible patients included details of the DVT diagnosis, risk factors for thrombosis, anticoagulation details, procedural and operative details for thrombolysis and rib resection, and diagnostic and interventional imaging reports.

Validated survey instruments were used to measure PTS severity and HRQoL scores.^{15,16} An initial phone call was made to all eligible patients to confirm their mailing address and inform them of the study. Survey instruments were then mailed only to eligible patients whose mailing address could be confirmed. A second mailing and 2 reminder phone calls were made to all nonresponders, 4 and 6 weeks after the initial mailing. All responders received a \$20 gift card for participation in the study.

Thrombophilia Testing

Thrombophilia testing following venous thromboembolism at NCH is individualized and usually includes antiphospholipid

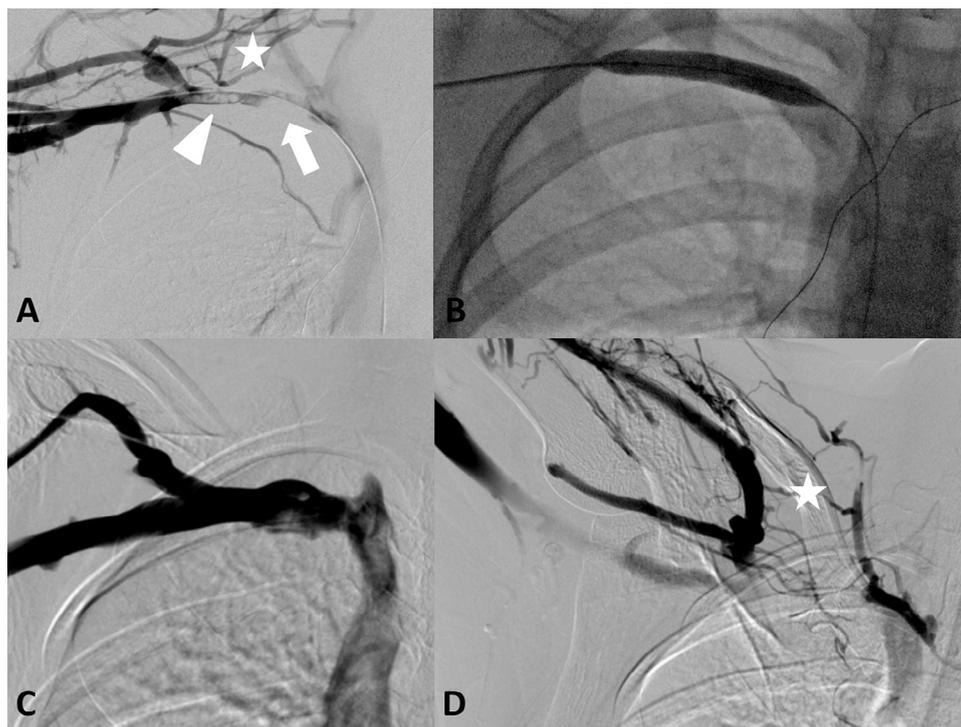


Figure 1. **A**, Digitally subtracted venogram images of the right upper extremity show filling defects within the central lumen of the subclavian vein (*white arrowhead*) consistent with acute thrombus. There is focal stenosis of the subclavian vein at the thoracic outlet (*white arrow*). Numerous well-formed collateral veins are evident (*white star*); **B**, an 8-mm angioplasty balloon has been placed into the right subclavian vein via right brachial vein access and inflated across the narrowed segment; **C**, repeat venogram images of the right upper extremity after venoplasty and pharmacomechanical thrombolysis show normal antegrade flow with resolution of intraluminal thrombus and subclavian vein stenosis; **D**, venogram images obtained with the right upper extremity placed in 180° abduction demonstrate pathologic compression of the subclavian vein at the thoracic outlet with diminished antegrade flow and filling of numerous collateral veins (*white star*).

antibodies (ie, lupus anticoagulant; IgG and IgM isotype anti-cardiolipin antibodies; IgG and IgM beta-2 glycoprotein-1 antibodies),¹⁷ factor V Leiden R506Q mutation, prothrombin gene G20210A mutation, antithrombin activity, protein C and protein S activity, fibrinogen level, FVIII, lipoprotein (a), and homocysteine levels.¹⁸ If performed, thrombophilia testing typically is completed at the time of DVT diagnosis and repeated at 3 months in case of abnormal results.

Bleeding Severity

Safety outcome definitions of bleeding were based on previously published recommendations from the Perinatal and Paediatric Haemostasis Subcommittee of the International Society on Thrombosis and Haemostasis.¹⁹ Bleeding episodes were categorized as “major” when bleeding was fatal; bleeding was associated with more than 2 g/dL decrease in the hemoglobin within a 24-hour period; retroperitoneal, pulmonary, or central nervous system bleeding; and when bleeding required surgical hemostasis in an operating room. In addition, clinically relevant nonmajor bleeding was defined as overt bleeding for which a blood product was administered and was not related to the patient’s underlying medical problem or bleeding that required medical or surgical intervention outside of the operating room. Lastly, “minor” bleeding was defined as any overt or macroscopic bleeding that did not fulfill the aforementioned criteria.

Survey Instruments

An iteration of a survey instrument that we previously developed and validated was used to assess the presence and severity of upper extremity PTS in children and young adults.^{15,20,21} The majority of the survey instrument was composed of the elements of the Kuhlke Scoring system, revised for self-administration.²² Questions on “paresthesia” and “pruritus” were incorporated from the Villalta instrument.²³ A question on “night cramps,” which has been reported previously as a symptom of PTS in both adult and pediatric studies, was incorporated.^{24,25} For the purpose of this study, only the self-report module of the instrument was used. The instrument assessed current signs (5 items) and symptoms (5 items) of PTS using a dichotomous scale for measuring response (yes [score: 1] and no [score: 0]), with the exception of venous ulceration (score 9). The summated score was categorized as mild (score: 1-3), moderate (score: 4-8), and severe (score: ≥ 9) PTS, in accordance with the Kuhlke instrument.^{15,22}

The PedsQL 4.0 is a multidimensional, 23-item questionnaire that has been validated in both healthy and sick children.^{16,26} It assesses physical (8 items), emotional (5 items), social (5 items), and school functioning (5 items). Again, for the purpose of this study, only the self-report module was used. All items use a 5-point Likert scale designed to assess level of functioning. Respondents report how often they experience a specific problem, grouped by functional domain (0: never a problem; 1: almost never; 2: sometimes; 3: often; and 4: almost always a problem). Items are reverse scored and linearly transformed to a 0-100 scale, such that greater scores indicate better HRQoL.²⁰ Two summary scores (total and psychosocial) can

be calculated based on the average of these domains. The general population will report scores in the individual domains ranging from 77 to 89.²⁷ Appropriate permissions to use both survey instruments were obtained.

Statistical Analyses

Standard statistical methods were used to summarize the data: frequency and percent for categorical measures and mean (SD), median (range) for continuous scaled measures. To compare outcome measures between patients who underwent thrombolysis and those who did not, the nonparametric Mann-Whitney *U* test was used. Analyses were performed using the base-R software package (R Foundation for Statistical Computing, Vienna, Austria). All calculated *P* values were 2-sided, and *P* values $<.05$ were considered statistically significant.

Results

Study Cohort and Management Details

Twenty-two subjects (12 female) were eligible for the study. Median age (range) at DVT diagnosis and survey completion were 16.3 (13.5-18.2) and 20.4 (13.7-24.2) years, respectively. Nineteen (86%) subjects reported a history of repeated overhead/strenuous activities (Table I; available at www.jpeds.com), and 12 of 17 (71%) events involved the dominant arm (dominant arm was unknown for 5 patients). Median interval between symptom onset and radiologic diagnosis was 2 (0-34) days. Imaging modalities used to make the diagnosis included Doppler ultrasound ($n = 21$) and magnetic resonance imaging ($n = 1$). Sixteen (73%) subjects had occlusive thrombosis, and 6 of 22 (27%) subjects had partially occlusive thrombosis at diagnosis. All patients underwent individualized thrombophilia testing, and 8 subjects were found to have a congenital/acquired thrombophilia. Additional risk factors for thrombosis are summarized in Table II (available at www.jpeds.com). Baseline demographic details are summarized in Table III.

With regard to management, all patients were treated with therapeutic anticoagulation and decompressive first and/or cervical rib resection with external venolysis surgery via a transaxillary approach. Median time interval between DVT diagnosis and surgery was 52 (12-442) days. All patients initiated therapeutic anticoagulation with low molecular weight heparin (target anti-FXa level: 0.5-1 units/mL), and 10 of 22 patients transitioned to warfarin (target international normalized ratio: 2-3).²⁸ Median duration of anticoagulation was 97 (42-440) days. Ten (45%) patients underwent upfront thrombolytic therapy (9 patients had catheter-directed thrombolysis and 3 patients had pharmacomechanical thrombolysis; Angiojet [$n = 3$]). Catheter-directed thrombolysis was performed through an infusion catheter placed in the interventional radiology suite. Recombinant tissue plasminogen activator (dose 0.03 mg/kg/h [maximum dose 2 mg/h]) was infused directly into the thrombus.²⁹ All patients received fixed-dose unfractionated heparin (10 μ /kg/hr) during thrombolysis per institutional guidelines. Complete blood count, activated partial thromboplastin time, prothrombin time,

Table III. Baseline demographic information

Characteristics	All patients
Total patients	22
Age at diagnosis, y, median (range)	16.3 (13.5-18.2)
Age at survey completion, y, median (range)*	20.4 (13.7-24.2)
Sex, male, n (%)	10 (45)
Dominant-arm DVT, n (%) [†]	12 (71)
History of repeated overhead/strenuous activities, n (%)	19 (86)
Pulmonary embolism present, n (%)	4 (18)
Days from symptom onset to diagnosis, median (range)	2 (0-34)
Symptoms at presentation, n (%)	
Swelling	22 (100)
Pain	16 (73)
Color changes	17 (77)
Paresthesia	5 (23)
Any thrombophilia present, n (%)	8 (36)
Factor V Leiden heterozygosity	4 (18)
Protein S deficiency	3 (14)
Antiphospholipid antibody syndrome [‡]	2 (12)
Elevated lipoprotein (a) [‡]	1 (50)

*Data available for survey responders (n = 19).

[†]Data only available for 17 patients.

[‡]Lipoprotein (a) levels were tested in only 2 patients.

fibrinogen, and d-dimer were checked every 4-6 hours during thrombolysis. Venography was repeated every 24 hours to assess residual thrombus burden. Median time interval between diagnosis and initiation of lytic therapy was 2 (1-9) days. Median duration of catheter-directed thrombolysis was 48 (24-72) hours. Post-thrombolysis venogram showed complete thrombus resolution in 7 of 10 subjects, partial resolution in 1 subject, and persistent occlusive thrombus in 2 of 10 subjects. Of note, only 2 of 14 patients diagnosed with PSS before 2013 underwent thrombolysis, whereas all 8 patients diagnosed with PSS after 2013 underwent an endovascular intervention. Thrombolysis was well tolerated, with no major/clinically relevant nonmajor bleeding reported. Nine patients (41%) also underwent balloon angioplasty post-thrombolysis for residual stenosis. Four (18%) patients experienced perioperative complications with rib-resection surgery, including minor

bleeding/local hematoma formation (n = 3), pneumothorax (n = 3), and winged scapula (n = 1).

Radiologic Outcome

Median time interval between DVT diagnosis and follow-up imaging was 93 (2-205) days for the entire cohort. Nineteen (86%) patients had complete thrombus resolution, 1 (5%) patient had partial resolution, and 2 (9%) patients had residual-occlusive thrombus on imaging. There was no significant difference in thrombus resolution rates between patients who underwent thrombolysis and those who did not (**Table IV**). No patient had recurrent DVT.

PTS Scores

We were unable to confirm the mailing address for 2 patients. The survey instruments were therefore mailed to 20 eligible patients. Nineteen (95%) patients responded to the survey instrument. Median time interval between DVT diagnosis and survey completion was 4 (0.3-7.3) years for the entire cohort and was significantly longer for patients who had not undergone thrombolysis (5.6 vs 2.1 years; $P = .01$).

Fourteen (74%) of the 19 survey responders reported signs/symptoms of PTS. Twelve (63%) respondents reported mild PTS, whereas 2 (11%) responders reported moderate PTS. Pain (n = 6) and paresthesia (n = 6) were the most commonly reported clinical symptoms of PTS, whereas swelling (n = 8) and dilated collateral vessels (n = 5) were the most commonly reported physical signs. Median PTS score for the entire cohort was 2 (0-5) and was not significantly different between patients who underwent thrombolysis and those who did not (**Table IV**). In fact, both patients reporting moderate PTS scores had undergone thrombolytic therapy.

HRQoL Scores

Median total HRQoL score for the survey respondents was 90.6 (73.9-100). Median physical and psychosocial HRQoL scores were 96.7 (81.3-100) and 93.3 (60-100), respectively. There was no significant difference between the HRQoL scores between

Table IV. Clinical characteristics of patients with PSS who did or did not receive thrombolysis before decompressive surgery

Characteristics	All patients	Thrombolysis	No thrombolysis	P values
Total patients, n	22	10	12	
Median age at diagnosis, y	16.3 (13.5-18.2)	16.2 (13.5-18.2)	16.3 (14.2-18.0)	.8
Median BMI at diagnosis	22.9 (17.5-34.6)	23.8 (20.0-32.8)	22.9 (17.5-34.6)	.9
Any thrombophilia, n (%)	8 (36)	5 (50)	3 (25)	.4
Occlusive thrombus at diagnosis, n (%)	16 (73)	8 (80)	8 (67)	.4
Symptom onset to diagnosis, d, median (range)	2 (0-34)	2 (0-34)	2 (0-7)	.3
Symptom onset to surgery, d, median, (range)*	54 (14-443)	40 (14-90)	71 (29-443)	.04
Median duration of anticoagulation, d	97 (42-440)	98 (91-205)	94 (42-440)	.8
Complete or partial resolution, n (%)	20 (91)	9 (90)	11 (92)	.9
Diagnosis to follow-up imaging, d, median (range)	93 (2-205)	92 (2-205)	94 (41-191)	.5
Median PTS score [†]	2 (0-5)	1 (0-5)	2 (0-3)	.7
Diagnosis to survey completion, y, median (range) [‡]	4 (0.3-7.3)	2.1 (0.3-6.3)	5.6 (3.8-7.3)	.01

BMI, body mass index.

*Patients undergoing thrombolysis underwent decompressive rib-resection surgery sooner than those who did not undergo thrombolysis, suggesting an institutional shift over the years to perform the definitive surgery shortly after diagnosis.

[†]Data only available for survey responders (n = 19).

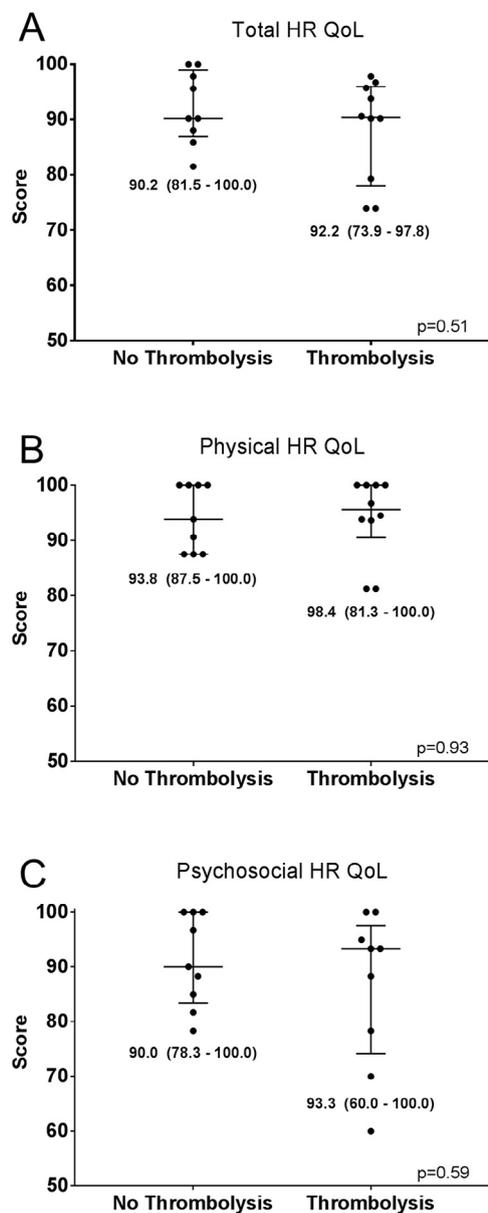


Figure 2. **A**, Median (range) total HRQoL scores in patients who underwent thrombolysis and those who did not; **B**, median (range) physical HRQoL scores in patients who underwent thrombolysis and those who did not; **C**, median (range) psychosocial HRQoL scores in patients who underwent thrombolysis and those who did not.

patients who underwent thrombolysis and those who did not (Figure 2).

Discussion

We report a large pediatric cohort of PSS who were managed using a standardized treatment protocol. Recruitment of an interventional radiologist with extensive catheter-directed thrombolysis experience in adults drove a practice change at

our institution in 2013. This provided us the opportunity to do a nonrandomized comparison between a historical control group of patients treated with anticoagulation and decompressive rib-resection surgery alone and a “thrombolysis” group. PSS was diagnosed in the second decade of their life, with a similar distribution between sexes. Most patients reported a history of repeated overhead activities, with baseball/softball pitching being the most commonly reported activity. Clot resolution on radiographs and HRQoL scores across the cohort were excellent. Although 74% of the survey responders reported having some symptoms/signs of PTS, only 11% reported having clinically significant, moderate PTS.²⁰ Thrombolytic therapy did not have a significant impact on clot resolution, as shown on radiographs, PTS scores, or HRQoL scores.

Effort-induced upper extremity DVT was first described in 1875 by Sir James Paget, who called it “gouty phlebitis.” In 1884, Leopold von Schroetter from Vienna described upper extremity DVT in a young painter and hypothesized that the muscular strain caused by repeated overhead activity was responsible for the thrombosis.³⁰ The term “Paget–Schroetter syndrome” was used in 1948 by Edward Hughes, who reviewed 320 patients with this condition.³¹ Management of PSS has evolved over the last several decades. Initially, anticoagulation was considered the “standard of care” for PSS. Unfortunately, early studies reported a high rate of obstruction on radiography, persistent symptoms, and permanent disability with anticoagulation alone.³² With the advent of thrombolytic agents, thrombolysis was hypothesized to be a powerful adjuvant to anticoagulation. However, as elaborated in a study by Lee et al, 45% of patients treated with thrombolysis and anticoagulation were noted to have persistent symptoms at end of therapy. In addition, 23% of patients who were asymptomatic at end of therapy developed recurrent thrombosis within a year of stopping anticoagulation.³³ Placement of venous stents was associated with a high rate of stent fracture and thrombosis.³⁴

In 1993, Machleder reported 36 adult patients with PSS treated with thrombolysis, 3 months of anticoagulation, and rib-resection surgery through a transaxillary approach.⁶ Radiologic and clinical outcomes across the cohort were excellent. These initial observations recently were confirmed in a systematic review reported by Lugo et al; 684 adults from 12 cohort studies were included in the final analysis.³⁵ Patients treated with thrombolysis and anticoagulation alone had 55% and 63% rate of venous patency and symptom resolution, respectively. In contrast, patients who also underwent first rib resection (with or without angioplasty) had a 88%-98% rate of venous patency and 93%-95% rate of symptom resolution. The exact timing of decompressive surgery remains a topic of debate, although studies in adults have shown that early surgery (performed shortly after thrombolysis) followed by 3 months of anticoagulation is as safe and efficacious as delaying surgery for 3-months.^{36,37}

In contrast to the extensive adult literature, pediatric data on PSS include single-institution, retrospective case series with 2-21 patients.^{5,7-11,38} Based on these data, we know that PSS tends to occur in the second decade of life, occurs equally in boys

and girls, and is often associated with repeated overhead activities. Recent data have shown that a multidisciplinary approach including thrombolysis, decompressive rib-resection surgery, and anticoagulation is associated with clot resolution on radiographs.⁵ Unfortunately, most of these studies did not systematically investigate PTS scores or HRQoL. Avila et al investigated PTS in 158 children with upper extremity DVT; 23 patients had unprovoked thrombosis, of which 20 were thought to have PSS.³⁹ In total, 8 of 23 patients underwent thrombolysis and 3 of 20 patients underwent decompressive surgery (personal communication, Suzan Williams, MD, The Hospital for Sick Children, 2017). At the time of last follow-up, 92% of patients reported PTS, of whom 26% reported moderate, clinically significant PTS. Our data confirm that a multidisciplinary approach for management of PSS in children is safe and associated with excellent radiologic outcomes. In addition, it shows a low rate of moderate PTS (11%) and excellent long term HRQoL scores.

A major limitation of our study was the small sample size. This study was not powered to investigate the impact of thrombolysis on patient outcomes. Based on a 25% reported rate of moderate-to-severe PTS in children with PSS treated with anticoagulation alone, and assuming a 15% reduction with thrombolysis, we estimate that ~100 patients would be required in each arm to adequately power a randomized-controlled trial (to achieve 80% power and with 2-sided alpha of 0.05) of thrombolysis for this condition. An additional limitation was the use of survey instruments to quantify PTS and HRQoL scores. Of note, both survey instruments have been validated prospectively and used previously in children with DVT and PTS.^{20,21} In addition, we had a remarkably good response rate to the survey instrument, with only 1 patient neglecting to respond.

Our study does raise an important question about the utility of upfront thrombolysis in patients with PSS. The need for thrombolysis has been debated in studies in adults. Guzzo et al published the experience at Johns Hopkins with 110 first rib resection and scalenectomy procedures performed in 103 adults.¹² In total, 45 surgeries were preceded by endovascular interventions, whereas 65 surgeries were preceded by anticoagulation alone; 91% of subclavian veins were patent in patients completing follow-up in both groups. In addition, most patients were asymptomatic at follow-up and had returned to their baseline activity levels. Ryan et al reported on 60 decompressive surgeries performed in 59 patients with PSS; use of upfront thrombolysis was not associated with improved radiologic outcomes.¹³ A randomized controlled trial investigating the role of thrombolysis would be ideal; however, given the rarity of PSS, attempting such a study may be predictably futile in the absence of a multi-institutional study network over a prolonged enrollment period.

In summary, children with PSS treated with decompressive first rib-resection surgery and anticoagulation have excellent radiologic and HRQoL outcomes. Although a significant proportion of patients report some symptoms or signs of PTS, only a small proportion report clinically significant moderate PTS. The need for upfront thrombolysis remains incompletely resolved. ■

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Table I. Overhead/strenuous activities reported by the cohort

Overhead/strenuous activities reported*	n
Baseball/softball pitching	9
Wrestling	5
Swimming	2
Volleyball	2
Football	2
Lacrosse, dance, basketball, shotput	1 each

*Five patients had more reported >1 overhead/strenuous activity.

Table II. Additional risk factors for thrombosis

Characteristics	n (%)
Overweight/obese	9 (43)
Oral contraceptive pill use	3 (25)*
Trauma	2 (9)
Tobacco use	1 (5)

*Only female patients.