Preliminary Investigations Showing Venous Thromboembolism Recurrence in Patients with Residual Venous Obstruction in Singaporean Population

Ashish Anil Sule, MD, MRCP, FRCP, FAMS, FICA, ESH¹ Chaozer Er, MRCP, FAMS¹
 Claudia Y.X. Chong, MBBS¹ Han Xin Chin, MBBS, MRCP¹ Tay Jam Chin, MRCP, FRCP, FAMS¹

¹ Department of General Medicine, Tan Tock Seng Hospital, Singapore, Singapore

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Address for correspondence Ashish Anil Sule, MD, MRCP, FAMS, FRCP, FICA, ESH Specialist, Department of General Medicine, Tan Tock Seng Hospital (TTSH), Singapore 575575, Singapore (e-mail: ashishsule@yahoo.com).

Abstract

This study aims to determine the association of residual venous obstruction (RVO) with recurrent venous thromboembolism (VTE). A retrospective cohort study was conducted determining if RVO on ultrasonography is associated with recurrent VTE in a Singaporean population. The subjects were identified from the Vascular Diagnostic Laboratory patients' record of Tan Tock Seng Hospital (TTSH), Singapore between 2008 and 2013. All the patients included had RVO after 3 months of anticoagulation. Data such as age, gender, race, thrombus location, etiology, history of malignancy, thrombophilia screen, treatment duration, and follow-up were recorded for analysis. Statistical analysis was performed using Stata/SE 13.1 (StataCorp LLC). The study was approved by the National Healthcare Group Domain Specific Review Board (DSRB), Singapore. Out of the 34 patients who had RVO, 6 (17.6%) developed VTE recurrence. Patients were treated with anticoagulation for a mean time of 24.5 months. The mean follow-up time for VTE recurrence was 25.4 months. Out of the six patients who had VTE recurrence, one had common iliac vein involvement, four had superficial femoral vein and common femoral vein involvement, zero had popliteal vein involvement, and one had calf veins involvement. There was a significant association between thrombophilia ($p = 0.0195$) and malignancy ($p = 0.020$) at inclusion with the risk of recurrent VTE. The presence of RVO after 3 months of anticoagulation is likely to increase the risk of VTE recurrence. Larger studies with RVO are needed to evaluate if there is an increased risk of VTE recurrence in the Asian population.

Keywords

- DVT
- recurrence
- residual vein thrombosis
- malignancy
- venous thromboembolism
- thrombophilia
- anticoagulation

Many factors such as malignancy, thrombophilia, male gender, age, thrombus location, provoked versus unprovoked deep vein thrombosis (DVT), D-dimer elevation, and high body mass index have been studied as potential risk factors for venous thromboembolism (VTE) recurrence.¹ It is uncertain if a residual venous obstruction (RVO) can reliably predict VTE recurrence as different studies have produced different results.¹ The aim of our study is to determine if an

RVO on compression ultrasonography (CUS) is associated with recurrent VTE in a Singaporean population.

Methodology

This is a retrospective cohort study which aims to determine if RVO on ultrasonography is associated with recurrent VTE in Singaporean population. In the study, patients

were treated according to the American College of Chest Physicians (ACCP) clinical practice guidelines on antithrombotic and prevention of thrombosis.² Patients with DVT secondary to a transient risk factor were treated with 3 months of anticoagulation; patients with idiopathic DVT were treated with at least 3 months of anticoagulation; patients with DVT secondary to malignancy or who had thrombophilia were treated with long-term anticoagulation therapy.²

Residual venous thrombosis was defined as the thrombus remaining the same or smaller using CUS after 3 months (or more) of anticoagulation. Recurrence was defined as the initial thrombus increasing in size or thrombus at a new site detected using CUS after 3 months or more. Complete resolution was defined as the resolution of the index thrombus using CUS after 3 months or more.

The subjects of our study were identified from our Vascular Diagnostic Laboratory patients' record. The patients who were included were registered with the Department of General Medicine, TTSH, Singapore between 2008 and 2013. Those patients included had a first episode of DVT, provoked or unprovoked, with or without pulmonary embolism, confirmed using CUS examination of the whole of the deep venous system of the lower limb, including the deep calf veins and subsequently after treatment with anticoagulation had RVO.

The technique which was used was similar to the Prandoni technique.¹ On the compressibility scan, a compressible vein was considered normal. If the vein could only be compressed partially, it suggested the presence of thrombus. On the longitudinal colored Doppler study, a normal biphasic pattern suggested that the vein had no thrombosis. If there was diminished phasicity, it suggested the presence of thrombus at that particular site. If there was a loss of phasicity, it suggested an occlusion, either by thrombosis or by a tumor occluding the vein, at a proximal site. VTE was diagnosed when the veins were not completely compressible, showing filling defects with pulsed and color Doppler interrogation. Computed tomography pulmonary angiography was done if pulmonary embolism (PE) was suspected at initial presentation.

The presence of thrombophilia, malignancy, prolonged immobilization, recent trauma, recent surgeries, recent pregnancy, and drug history, in particular, oral contraceptive pills and hormone replacement therapy were recorded. These patients were followed up with the Department of General Medicine Vascular Clinic for a minimum of 3 months. All the patients received the standard management for DVT in our institution. Patients were treated with a minimum of 5 days with low-molecular-weight heparin, for example, enoxaparin (1 mg/kg) subcutaneous injection twice daily. Warfarin was also commenced on the day of diagnosis and heparin therapy was discontinued after 5 days or when the international normalized ratio was in the therapeutic range of 2 to 3. Warfarin therapy was continued in accordance with the latest ACCP guidelines.

Repeat ultrasonography was performed after 3 months of warfarin therapy, using the same ultrasound technique as

illustrated above. Patients with RVO were included in our study.

The following patients were excluded from our study.

1. Patients who were not followed up with the Department of General Medicine, TTSH
2. Patients whose index event was a PE without DVT
3. Patients whose index DVT resolved after 3 months of anticoagulation therapy with no RVO
4. Patients whose index DVT event was at a site other than that of the lower limbs such as the upper limbs or the superior mesenteric vein
5. Patients whose index DVT event was treated with an inferior vena cava (IVC) filter
6. Patients who were lost to follow-up

Data such as age, gender, race, thrombus location, etiology of the DVT, history of malignancy, thrombophilia screen, treatment duration, and follow-up period for DVT were recorded for analysis.

Statistical analysis was performed using Stata/SE 13.1 (StataCorp LLC). Subjects were classified into those with and without RVO. Those with RVO were followed up for a minimum of 1 year to monitor for VTE recurrence. The incidence of recurrent VTE was then recorded and stratified for confounders, to determine if the presence of RVO increased the risk of VTE recurrence. Cox proportional hazards were used to assess the significance of potential risk factors on time to recurrence, and results were reported as hazard ratios with 95% confidence intervals. A *p* value <0.05 was considered statistically significant.

The study was approved by the National Healthcare Group DSRB, Singapore.

Results

A total of 50 patients from the Vascular Diagnostic Laboratory, TTSH, had a confirmed first-lifetime diagnosis of DVT with RVO between January 2008 and December 2013. Of the 50 patients, 7 were excluded from the study as they were admitted to other departments, 2 were excluded as they had a DVT of the upper limb, 1 was excluded as the DVT was located in the superficial mesenteric vein, 2 were excluded as they had IVC filters inserted, and 4 were excluded as they were lost to follow-up. The 34 patients who met the inclusion criteria were analyzed in our study. Their mean $\pm$ standard deviation (SD) age at onset was 66.9 ± 14.5 years. A total of 20 patients were females (58.8%), and 14 were males (41.2%). Overall, 30 patients were Chinese (88.2%), 2 patients were Malay (5.9%), and 2 were Indian (5.9%). Of the total index DVT cases, 21 (61.7%) were provoked while 13 (38.2%) were unprovoked. A total of 16 patients (47.1%) involved the common femoral vein or superficial femoral vein, 11 (32.4%) involved the common iliac vein, 4 (11.8%) involved the popliteal vein, and 3 (8.8%) involved the calf vein.

All patients received standard DVT treatment. The mean $\pm$ SD durations of oral anticoagulation therapy was 24.5 ± 3.7 months. The patients were followed up with the

Department of General Medicine, Vascular Medicine Anticoagulation Clinic for a mean $\pm$ SD of 25.4 ± 2.4 months.

Bivariate analysis followed by multivariate analysis was performed to determine whether the various factors such as gender, race, veins involved, provoked or unprovoked DVT, the presence of malignancy or thrombophilia, treatment duration and follow-up duration increased the risk of recurrent VTE.

Among the 14 males included in the study, 3 (21.4%) had recurrent VTE while among the 20 females, 3 (15.0%) had recurrent VTE. With regards to race, 5 out of 30 Chinese (16.7%), 1 out of 2 Malays (50.0%), and 0 out of 2 Indians (0%) had recurrent VTE. With regards to thrombus location for index DVT event, 1 out of 11 patients with common iliac vein thrombus (9.8%), 4 out of 16 patients with superficial and common femoral vein thrombus (25.0%), 0 out of 4 patients with popliteal vein thrombus (0%), and 1 out of 3 patients with calf veins thrombosis (33.3%) developed recurrent VTE. The patient with an index calf vein DVT had a recurrence involving the common iliac vein. A possible reason for patients with common iliac vein DVT having significantly lower percentage of recurrence than patients with superficial/common femoral vein and calf vein DVT was the treatment duration (►Table 1). In this study, it was noted that patients with common iliac vein thrombus had the longest duration of treatment in months (mean: 29, range: 6–48), superficial femoral and common femoral veins (mean: 11.8, range: 3–36), popliteal vein (mean: 18.8, range: 3–27), calf vein (mean: 9, range: 3–18). Multivariate analysis showed that there was a significant association between

thrombophilia and malignancy and the risk of recurrent VTE. Of the five patients who had thrombophilia at presentation, three (60%) had a recurrent VTE. Of the three patients who had malignancy at presentation, two (66.7%) had a recurrent VTE (►Table 2).

Discussion

There are many definitions of RVO.¹ According to Prandoni et al, at maximal compression, if the compressed vein's diameter was >2 mm when a single test was performed or if the compressed vein's diameter was >3 mm in two consecutive compression measurements, RVO was considered present.¹ Siragusa et al¹ defined the presence of RVO as a compressed vein's diameter $>40\%$ of the noncompressed vein's diameter. Le Gal et al¹ came out with the third definition which classified RVO degree into five categories: mild RVO with normal compression ultrasound appearance, minimal wall thickening (5% or less of maximal vein diameter), partial resolution (40% or more of the vein's diameter was compressible), minimal resolution (less than 40% of the vein being compressible), and stable/worsened thrombus. Combining Siragusa's and Prandoni's definitions, Poli et al¹ defined RVO by the presence of either a compressed diameter of $>40\%$ of the noncompressed venous diameter or an absolute compressed venous diameter of >2 mm. Prandoni's definition was applied in our study.

Surveillance CUS after initial diagnosis of lower limb DVT can assess the thrombus progression in patients who have been unable to receive anticoagulation treatment.¹ It also

Table 1 Bivariate analysis: Recurrence (%)

Factor		N (%)
Gender	Male	3 out of 14 (21.4%)
	Female	3 out of 20 (15.0%)
Race	Chinese	5 out of 30 (16.79%)
	Malay	1 out of 2 (50.0%)
	Indian	0 out of 2 (0%)
Veins involved	Common iliac vein	1 out of 11 (9.9%)
	Superficial femoral vein/common femoral vein	4 out of 16 (25.0%)
	Popliteal vein	0 (0%)
	Calf vein	1 out of 3 (33.3%)
Etiology	Thrombophilia	3 out of 5 (60%)
	Malignancy	2 out of 3 (66.7%)
Deep vein thrombosis	Provoked	2 out of 21 (9.5%)
	Unprovoked	4 out of 13 (30.8%)
Treatment duration	≤ 1 y	2 (10.5%)
	> 1 y	4 (26.7%)
Follow-up duration	≤ 1 y	1 (16.7%)
	> 1 y	4 (26.7%)

Table 2 Multivariate regression analysis and hazard ratio for recurrent venous thromboembolism

Factors	Hazard ratio	95% Confidence interval	p Value
Thrombophilia	13.0	1.5–111.8	0.0195
Malignancy	13.5	1.0–185.5	0.020
Provoked/unprovoked	4.2	0.6–27.5	0.1319
Treatment duration (≤ 1 y vs. > 1 y)	3.1	0.5–19.8	0.2342
Follow-up duration (≤ 1 y vs. > 1 y)	7.7	0.8–75.3	0.0784

helps to form a new baseline which is helpful for recurrent VTE assessment or diagnosis in the future.² Detection of RVO is another potential use as RVO may increase the risk of VTE recurrence.¹

Different studies assessing the role of RVO as a predictor of VTE recurrence has generated different results. Stephenson et al¹ published a recent meta-analysis (included six articles) that showed that RVO is a mild risk factor for VTE recurrence.¹ A prospective cohort study performed by Cosmi et al¹ showed that the RVO+ group had a higher VTE recurrence rate, but that was not statistically significant. Poli et al¹ performed a prospective cohort study that showed similar VTE recurrence rate between RVO+ and RVO– groups.¹ PROLONG and REVERSE study did not find a significant difference in VTE recurrence rate in RVO+ and RVO– groups.¹ The Duration of Anticoagulation based on Compression Ultrasonography (DACUS) study found a significantly higher risk of VTE recurrence in RVO+ patients who were given 3 months of anticoagulation versus those RVO+ patients treated with 12 months of anticoagulation.¹ The extended DACUS study showed that RVO+ patients treated with 2 years of anticoagulation had higher VTE recurrence than the RVO– group despite the longer duration of anticoagulation therapy.¹ The DACUS and extended DACUS trials were the main determinants of significant differences in VTE recurrence between RVO+ and RVO– in this meta-analysis.¹ They also observed very low rate of VTE recurrence (1.3–1.5%) in RVO– group compared with our studies.¹

Also, Carrier et al¹ published a meta-analysis that showed that RVO was mildly predictive of recurrent VTE when provoked and unprovoked DVT cases were analyzed together.¹ However, the association was absent when only unprovoked DVT cases were evaluated.¹ Tan et al performed a meta-analysis that found the modest risk of VTE recurrence in patients with RVO, but the association was heterogeneous and dependent on many variables.¹ Donadini et al in their meta-analysis identified RVO, age and male gender to be significant predictors of VTE recurrence.¹ There were significant heterogeneities of the many RVO-related studies, such as different RVO definitions, variable timing of repeat CUS to assess RVO, the inclusion of provoked and unprovoked VTEs, and the location of index DVT was not consistently reported in some articles.¹

Our study showed that the RVO+ patients had a VTE recurrence rate of 17.6%. One limitation of our study was we did not have the data on VTE recurrence rate in RVO– patients as they were excluded. We, however, have compared the VTE recurrence rate in RVO– patients in DACUS study and another study done in Korea. The DACUS study observed the very low rate of VTE recurrence in patients without RVO, and it was one of the main drivers of statistically significant increased VTE recurrence risk in RVO+ patients.¹ In DACUS study, the recurrence rate of VTE was 23.3 and 1.3% in RVO+ and RVO– group, respectively.¹ In a study conducted in Korea, the cumulative percentage of VTE recurrence in RVO+ and RVO– groups was approximately 10 and 5%, respectively, at 24 months, and RVO was concluded as a significant predictor of VTE recurrence in the study.³ Having compared with the percentage of VTE recurrence in RVO– groups in DACUS study and the Korean study, we concluded that RVO is highly predictive of VTE recurrence in Singaporean population. As all of the RVO+ patients in our study developed recurrent DVT after the cessation of anticoagulation, it is advisable to give long-term anticoagulation for this group of patients.

It is known that Asians have relatively low incidence and prevalence of VTE.³ Inherited thrombophilia mutations such as Factor V Leiden, and prothrombin G20210A are not found in Chinese, Japanese, or Taiwanese.³ These reflected the racial disparities in VTE. Clinical factors associated with VTE recurrence have also not been well studied in Asian populations.³ In a study done in Korea, 303 patients with newly diagnosed VTE were followed up to evaluate the risk factors for recurrent VTE events. The study concluded that independent predictors for recurrent VTE were residual thrombosis and antiphospholipid syndrome. Extended anticoagulation was advocated in these groups.³ In our study, the subjects were 34 Singaporeans consisted of 30 (88%) Chinese, 2 (6%) Indians, and 2 (6%) Malays. Our study showed that the presence of RVO was predictive of VTE recurrence in Singaporeans of which the majority was Chinese by ethnicity. More prospective studies should be done in the future to assess the predictors of VTE recurrence in the Asian population.

Other than VTE recurrence prediction, RVO at 3 months after anticoagulation for DVT was found to be associated with higher risk of postthrombotic syndrome (PTS), symptomatic arterial thrombotic events, and cancer.⁴ These were not

analyzed in our study. They, however, may have important implications in patients with DVT (provoked and unprovoked) and RVO:

1. Should cardiovascular risk estimation justify statin and/or antiplatelet therapy be performed routinely?
2. Should aggressive cancer screening, for example, computed tomography of abdomen/pelvis (CTAP) be performed routinely? (Knowing that CTAP did not provide significant benefit in patients with unprovoked DVT in terms of occult cancer diagnosis⁵)

Patients with cancer have four to sevenfold increased risk of VTE and are also two to three times more likely to have recurrent VTE compared with patients with no cancer.⁶ In our study, patients with a concurrent malignancy were 13.5 times as likely to have a VTE recurrence as compared with patients without a concurrent malignancy (odds ratio [OR]: 13.5, 95% confidence interval [CI]: 1.0–185.5, $p = 0.020$).

The 2009 AESOPUS study concluded that tailoring the duration of anticoagulation on the basis of ultrasonography findings of RVO reduces the rate of recurrent VTE in adults with proximal DVT.⁷ For our study, there was no significant association between treatment duration (≤ 1 vs. > 1 year) and VTE recurrence (OR: 3.1, 95% CI: 0.5–19.8, $p = 0.2342$). However, one of the main factors contributing to the lack of association could be probably small cohort size of RVT.

As repeat CUS at the end of anticoagulation to assess for RVO incurs the significant medical cost and our study is a retrospective cohort study with no direct comparison of VTE recurrence incidence in the RVO– patients, we are unable to make a recommendation about routine surveillance CUS to assess for RVO. More prospective randomized trials should be performed especially in Singaporean population to study the role of RVO in VTE recurrence prediction. The association

between RVO and malignancy, arterial thrombosis, and PTS also warrants further research.

Conclusion

The presence of RVO after 3 months of anticoagulation is likely to increase the risk of VTE recurrence. Larger studies with RVO are needed to evaluate if there is increased the risk of VTE recurrence in the Asian population.

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