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Interobserver reliability of compression ultrasonography for residual thrombosis after first unprovoked deep vein thrombosis

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ABSTRACT

Accurate assessment of residual thrombosis is of clinical importance for diagnostic baseline imaging, and may be of value in risk stratification for recurrent venous thromboembolism (VTE). This study evaluated the interobserver reliability of the measurement of residual thrombosis in patients 6 months after a first unprovoked deep vein thrombosis (DVT) of the leg.

All enrolled patients received two ultrasonography examinations by two independent blinded ultrasonography technicians 5–7 months after their first unprovoked DVT. In total, 49 patients completed the two baseline ultrasonography examinations. During the examinations, the presence of residual thrombosis was evaluated. If residual thrombosis was present, a detailed description of the size and location was reported. After all ultrasonographyresults had been collected, the interobserver agreement was calculated by use of the kappa statistics, Pearson correlation, and the Bland–Altman plot. Furthermore, the clinical implications of interobserver reliability were examined.

The interobserver reliability of the assessment of whether residual thrombosis is present was very good ($\kappa = 0.92$). The interobserver reliability of the measurement of residual thrombosis was good ($r^2 = 0.648$), with a limited number of patients being misclassified. For the assessment of the percentage of residual occlusion, the interobserver reliability was fair ($r^2 = 0.357$).

Our results suggest that the interobserver reliability for measurement of residual thrombosis is high, and that the variability introduced by interobserver reliability has minimal clinical implications. Our study is important for the use of baseline imaging for the diagnostic and prognostic management of recurrent VTE.

INTRODUCTION

Between 5% and 27% of patients with an unprovoked venous thromboembolic event will experience a recurrence in the year following discontinuation of anticoagulation, and up to 45% will experience a recurrence after 8 years.[1-4] Assessment of residual thrombosis after venous thromboembolism (VTE) appears to be of importance for the diagnostic management of future suspected events, and may be important for risk stratification for duration of anticoagulation, as it may be a predictor of recurrent VTE in patients with unprovoked VTE. Documentation of residual thrombosis on baseline imaging has also been shown to be beneficial for the diagnostic management of suspected recurrent VTE.[5] Baseline imaging could be performed after the discontinuation of anticoagulant therapy or after a predefined period of time following acute deep vein thrombosis (DVT). With baseline imaging, the presence or absence of residual thrombosis could be assessed, and, if present, the characteristics of the residual thrombosis could be reported and be useful for future suspected events.

The diagnostic management of ipsilateral recurrent DVT can be challenging, as the differentiation between residual and recurrent thrombosis is difficult to make. Distinguishing a recurrent thrombosis from a residual thrombosis is clinically important, because recurrent thrombosis requires indefinite anticoagulant therapy with the risk of fatal bleeding, whereas residual thrombosis does not. A previous study has shown that comparing imaging results at the time of suspected recurrence with baseline results is a valid approach to exclude recurrent VTE.[5,6] As one of the commonly used definitions of a thrombosis recurrence is an increase in thrombus diameter of 4 mm, an accurate report of residual thrombus diameter during compression is of high clinical importance.[7] Besides the importance of establishing the characteristics of residual thrombosis for baseline imaging, a debate exists about whether the presence of residual thrombosis is also associated with an elevated risk of recurrent VTE. A recent systematic review and meta-analysis showed that residual thrombosis was associated with a modestly increased risk of recurrent VTE in patients with a DVT.[8] Currently, the most frequently reported definitions of residual thrombosis are a thrombus diameter of ≥2 mm during full compression or residual vein occlusion of ≥ 40%.[9-11]

Given the importance of obtaining baseline imaging to accurately diagnose ipsilateral recurrent DVT and the potential role of baseline imaging in predicting VTE recurrence, the interobserver reliability of measurements of residual thrombosis need to be well documented. To date, little research has been performed on the interobserver reliability of measurements of residual thrombosis.

This study was aimed at ascertaining the interobserver reliability and the clinical implications of imperfect interobserver reliability. We sought to examine the interobserver reliability of different methods for the assessment of residual thrombus by ultrasonog-

raphyin patients with a first unprovoked DVT following 6 months of anticoagulant treatment.

MATERIALS AND METHODS

Study design and selection of participants

A prospective cohort study was performed, in which we included patients who had an objectively proven first proximal unprovoked DVT diagnosed 5.5–7 months before enrollment. All patients were treated initially with a minimum of 5 days of heparin or low molecular weight heparin and oral anticoagulants with a target intensity of 2.0–3.0. Patients were not eligible for the study if they had a recurrent VTE during the treatment period or were committed to long-term anticoagulant therapy.

Objective documentation of DVT required a non-compressible segment on compression ultrasonography of a proximal leg vein (trifurcation and/or higher).

We defined an unprovoked DVT as one that occurred in the absence of a leg fracture or lower-extremity plaster cast, immobilization for > 3 days or surgery with a general anesthetic in the 3 months before the index event, and without the diagnosis of a malignancy in the past 5 years.

We excluded patients who were unable or unwilling to provide written informed consent, were aged ≤ 17 years, had a recurrent idiopathic VTE (i.e.two or more previous idiopathic VTEs), had a known deficiency of protein S, protein C, or antithrombin, had known persistently positive anticardiolipin antibodies (titers > 30 U mL^{-1}) or positive lupus anticoagulant, or had combined thrombophilic defects (e.g. homozygous for factor V Leiden or prothrombin gene mutation (PGM), or compound heterozygous for FV Leiden and PGM). We obtained approval from the Ottawa Hospital Research Ethics Board.

Methods

All study patients underwent imaging at 5.5–7 months after their acute DVT episode. Imaging included two compression ultrasonography examinations of the affected limb(s) by two independent sonographers blinded to the index event (at the time of diagnosis) location and all previous ultrasonography results (clinically indicated or any study ultrasonography examinations). The ultrasonography machine used was a Phillips 5000 with a linear high-frequency probe (L7-4); the same ultrasonography unit was used during both examinations. The patients were instructed not to comment on any specifics of the previous ultrasonography examination(s). Standardized procedures were utilized for both ultrasonographyexaminations. The whole venous system (common femoral vein until the trifurcation) of both legs was assessed for the presence

of residual thrombosis. The sonographers independently recorded their findings on standardized ultrasonography case report forms. If residual thrombosis was present, the location, diameter, percentage of occlusion and distance of the proximal terminus to the sapheno-femoral junction (SFJ) were measured and reported.

ultrasonography examination

Patients were examined in a supine position with the head of the bed raised 20° or 30° to enhance venous filling in the legs. The following veins were consecutively examined at the following anatomic points: common femoral vein, SFJ, superficial femoral vein, popliteal vein, and the trifurcation. Distal leg veins were not imaged. The examined vein was imaged in a transverse plane. The distance between the anterior and posterior wall was measured with and without compression.

Residual thrombosis was defined as being present when the thrombus diameter was ≥ 2 mm during full compression. If residual thrombosis was present, the distance between the proximal terminus of the residual thrombosis and the SFJ was reported. The vein diameter was measured before and during compression, and the percentage of occlusion was calculated. The percentage of occlusion was calculated by dividing the vein diameter with compression by the vein diameter without compression multiplied by 100% (figure 1). Residual thrombosis is considered to be present if there is ≥40% occlusion; however, in this study, the sole criterion for the presence of residual thrombosis was incompressibility of a venous segment with a thrombus diameter of ≥ 2 mm.

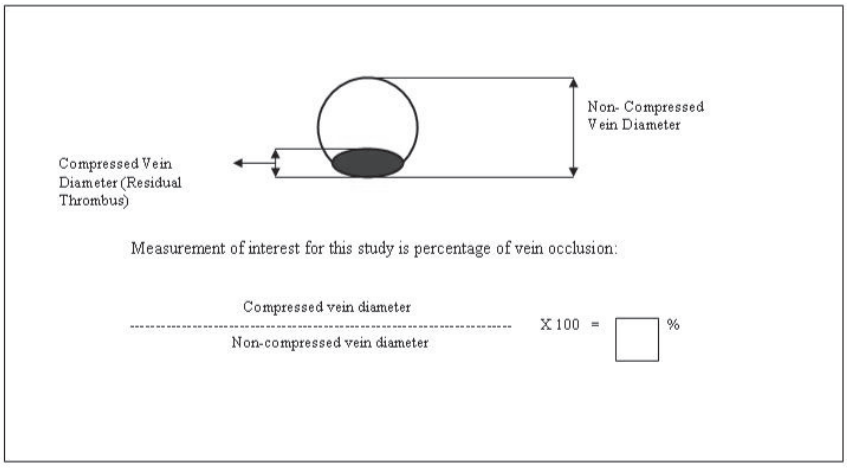

Figure 1 Explanation of the term residual occlusion

Statistical analysis

The interobserver agreement of each predictor variable was determined by calculating a two-rater unweighted kappa statistic, where κ is defined as:

$$\kappa = \frac{P_o - P_e}{1 - P_e}$$

Where Po is the actual probability of agreement Pe is the expected agreement by chance.

The Pearson coefficient of correlation for the continuous data was calculated. A kappa score or Pearson coefficient of correlation of 0.81–1.0 is considered to indicate very good reliability, a kappa score between 0.61 and 0.8 good reliability, a kappa score between 0.41 and 0.6 moderate reliability, a kappa score between 0.21 and 0.4 fair reliability, and a kappa score below 0.2 poor reliability.[12,13]

The Bland–Altman plot was used to assess agreement between the observers on all continuous data. We also used the Bland–Altman plot to determine the clinical implications of imperfections in interobserver variability. The cut-off for whether residual thrombosis was present or not was a thrombus diameter of ≥ 2 mm. We included a 'cut-off line' for the area where disagreement in measurements would have clinical implications (i.e. the presence or not of residual thrombosis). For example, if the mean thrombus diameter between two observers was 4 mm and in the case where one observer measured a thrombus diameter of 3 mm and the other a thrombus diameter of 5 mm, both observers would agree on the 'presence of residual thrombosis (≥ 2 mm).

However, with the same mean residual thrombosis of 4 mm, if one observer measured a thrombus diameter of 1 mm and the other a thrombus diameter of 7 mm, they would disagree on the presence of residual thrombosis (that is, one would classify a patient as having no residual thrombosis [thrombus diameter <2 mm] and the other would classify the patient as having residual thrombosis [thrombus diameter ≥ 2 mm]). In order to construct the line of clinically relevant disagreement, the border of clinically relevant disagreement lies when one observer measures a thrombus diameter of 1.9 mm. So, for example, in the case of a thrombus diameter mean of 4 mm, one observer measures a thrombus diameter of 1.9 mm (saying that residual thrombosis is absent), and the other observer measures a thrombus diameter of 6.1 mm (saying that residual thrombosis is present). The mean diameter difference cut-off point for the presence of residual thrombosis (i.e. clinically relevant disagreement) is therefore 6.1– 1.9 = 4.2 mm. So, if the mean thrombus diameter were 4 mm, differences between the measurements of > 4.2 mm would lead to the observers to disagree on the presence of residual thrombosis. In this way, we constructed the line that connects clinically relevant cut-off points for mean residual thrombosis diameter, and established the area where imperfection in interob-

server variability would have clinical implications. For all calculations, PASW statistics version 18.0.0 (IBM SPSS Inc, 2009, Chicago, IL, USA) was used.

RESULTS

Patients

During the study period (7 May 2006 to 9 April 2008), 114 patients were evaluated for eligibility. Of these patients, 34 refused or were unable to give informed consent, eight were on long-term anticoagulant therapy, and three had known persistently elevated antiphospholipids or anticardiolipins; in seven patients, the DVT diagnosis was made > 7 months previously, and in six patients the DVT was a recurrent episode. The remaining 56 patients were enrolled; seven patients withdrew consent after enrollment, leaving 49 patients for analysis. Of these patients, 31 were male (63.3%), and the mean age was 59 years (standard deviation [SD] 15 years).

Interobserver agreement on the presence of residual thrombosis

Among 49 patients, the two observers agreed that, in 19 patients, no residual thrombosis was present in any of the veins. The two observers agreed that residual thrombosis was present in 28 patients; disagreement on whether residual thrombosis was present occurred for two patients (Table 1).

Table 1. Interobserver variability in determining the presence of residual thrombosis (thrombus diameter ≥ 2 mm).

		Observer 2		
		No residual thrombosis (n)	Residual thrombosis (n)	Total (n)
Observer 1	No residual thrombosis (n)	19	2	21
	Residual thrombosis (n)	0	28	28
	Total (n)	19	30	49

N: number

The interobserver agreement on whether residual thrombosis was present or not was very good (κ = 0.92, 95% confidence interval [CI] 0.8–1). We also assessed the interobserver agreement for every venous segment separately (Table 2). For the common femoral vein, the two observers agreed that 44 patients did not have a residual thrombosis. The two observers also agreed on the presence of residual thrombosis in two patients. Disagreement existed for three patients. The point estimate of the kappa for measuring residual thrombosis in the common femoral vein was moderate (κ = 0.54, 95% CI 0.034–1). For the superficial femoral vein, the observers agreed that 28 patients were

Table 2. Interobserver variability in determining the presence of residual thrombosis (thrombus diameter ≥ 2 mm) in different venous segments.

		Observer 2		
		No residual thrombosis (n)	Residual thrombosis (n)	Total (n)
	Common femoral vein			
Observer 1	No residual thrombosis (n)	44	1	45
	Residual thrombosis (n)	2	2	4
	Total (n)	46	3	49
	Superficial vein			
Observer 1	No residual thrombosis (n)	28	2	30
	Residual thrombosis (n)	0	19	19
	Total (n)	28	21	49
	Popliteal vein			
Observer 1	No residual thrombosis (n)	26	5	31
	Residual thrombosis (n)	2	16	18
	Total (n)	28	21	49
	Trifurcation			
Observer 1	No residual thrombosis (n)	26	2	28
	Residual thrombosis (n)	1	20	21
	Total (n)	27	22	49

N: number

free of residual thrombosis. They agreed on the presence of residual thrombosis in 19 patients. Disagreement existed for two patients. The interobserver agreement reflecting the presence or absence of residual thrombosis was very good (κ = 0.92, 95% CI 0.8–1). For the popliteal vein, both observers agreed that 26 patients were free of residual thrombosis. The two observers also agreed on the presence of residual thrombosis in 16 patients.

Disagreement existed for seven patients. The point estimate of the kappa for measuring residual thrombosis in the popliteal vein was good (κ = 0.7, 95% CI 0.5–0.9). For the trifurcation, the two observers agreed that 26 patients were free of residual thrombosis. The two observers also agreed on the presence of residual thrombosis in 20 patients. Disagreement existed for three patients. The point estimate of the kappa for measuring residual thrombosis in the trifurcation was very good (κ = 0.88, 95% CI 0.74– 1.00).

Interobserver agreement on the measurement of residual thrombosis

All patients who were considered to have a residual thrombosis by either observer had a thrombus diameter during full compression of ≥ 2 mm, in accordance with the study protocol.

In patients who were considered to have a residual thrombosis, the mean vein diameter measured without compression by observer 1 was 8.03 mm (SD 2.3 mm), and that measured by observer 2 was 8.33 mm (SD 1.9 mm). The mean residual thrombosis diameter measured during full compression by observer 1 was 5.44 mm (SD 1.3 mm), and that measured by observer 2 was 5.99 mm (SD 1.8 mm). In 28 patients, both observers agreed on the presence of residual thrombosis (i.e. thrombus diameter of ≥ 2 mm); for the following analysis, we used the data of these patients. The Pearson coefficient of the correlation between the measurements of residual thrombosis during full compression by the two observers was 0.648 (P = 0.000), indicating a good correlation. The 95th percentile for the difference in measurements between the two observers was 2.0 mm. Table 3 shows the number of patients and corresponding percentages for the cut-off points for the difference in residual thrombus measurement between the observers. More than 20% of the paired measurements of the patients with a residual thrombosis differed by ≥ 1 mm.

We only had data on the thrombus diameter for patients in whom the observers measured residual thrombosis; therefore, we have imputed a thrombus diameter of 1.99 mm for patients who were considered to have no residual thrombosis, to conservatively examine the best case scenario of reliability, and a thrombus diameter of 0 mm to conservatively examine the worse case scenario of reliability. Figures 2 and 3 show the Bland–Altman plots.

In the best case scenario, where we imputed a thrombus diameter of 1.99 mm in patients who were not considered to have a residual thrombosis, the mean difference in thrombus diameter was 0.4 mm, with an SD of 1.29 mm (figure 2). In this case, three patients had a difference of > 2 SDs, and these were mainly in the larger clot sizes. If

Tabel 3. Differences in measurements between the two observers.

	Cut-off points	n (%)
Thrombus diameter measurements (mm)	≤ 0.5	10 (36)
	≤ 1	22 (79)
	≤ 2	26 (93)
Thrombus occlusion (%)	≤ 10	10 (36)
	≤ 15	18 (64)
	≤ 20	22 (79)
	≤ 25	23 (82)
Distance between proximal terminus of residual thrombosis and the SFJ (cm)	≤ 1	6 (30)
	≤ 2	10 (50)
	≤ 6	16 (80)
	≤ 10	18 (90)

SFJ: sapheno-femoral junction; n: number

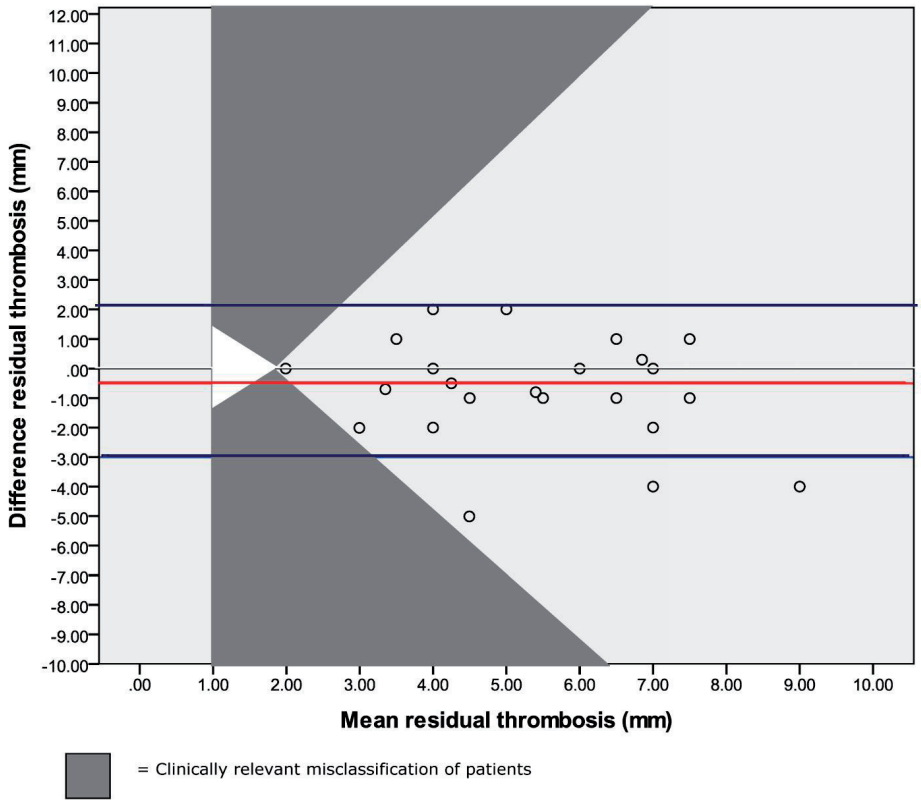

Figure 2. Bland–Altman plot for measurement of residual thrombosis diameter best case scenario (with 1.99 mm imputed for patients assessed as having no residual thrombosis). Red line: mean difference in thrombus diameter. Blue lines: two times standard deviation (2SDs).

we examine the clinical impact (i.e. whether patients would be misclassified because of observer variability), no patients (0%; 95% CI 0–7.2%) were in the gray 'misclassification' area, so none of the patients would be misclassified because of interobserver variability. In the worse case scenario, where we imputed a thrombosis diameter of 0 mm in patients who were not considered to have a residual thrombosis (Fig. 3), the mean difference in thrombus diameter was 0.5 mm (SD 1.5 mm), and two patients (4%; 95% CI 1–14%) were located in the gray area, and would be misclassified because of interobserver variability. Therefore, between 0% and 4% of the patients would be misclassified because of interobserver variability.

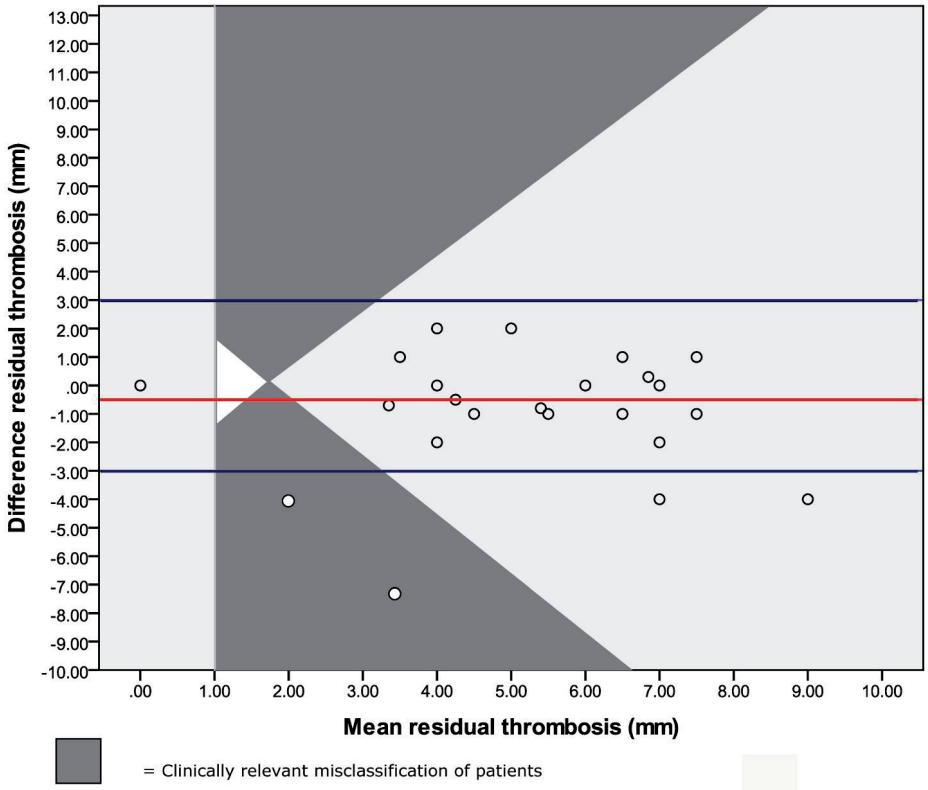

Figure 3 Bland–Altman plot for measurement of residual thrombosis diameter worse case scenario (with 0 mm imputed for patients assessed as having no residual thrombosis). Red line: mean difference in thrombus diameter. Blue lines: standard deviation.

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Interobserver agreement on occlusion percentage of the residual vein occlusion (used as a potential predictor of recurrent VTE)

Residual vein occlusion of ≥ 40% has been proposed in different studies as a potential predictor for recurrent VTE.[10, 11] In all patients for whom both observers agreed on the presence of residual thrombosis (thrombus diameter of ≥ 2 mm), the thrombus occlusion was ≥ 40%. In 28 patients, both observers agreed on the presence of residual thrombosis (i.e. thrombus diameter of ≥ 2 mm during full compression); for the following analysis, we used the data of these patients. The mean percentages of occlusion were 71.56% (SD 16.8) for observer 1 and 71.60% (SD 15.9) for observer 2.

The Pearson coefficient of the correlation between the percentage assessments of both observers was 0.357 (P = 0.062), indicating a fair, but not statistically significant, correlation. Figure 4 shows the Bland–Altman plot. On average, the two readers differed

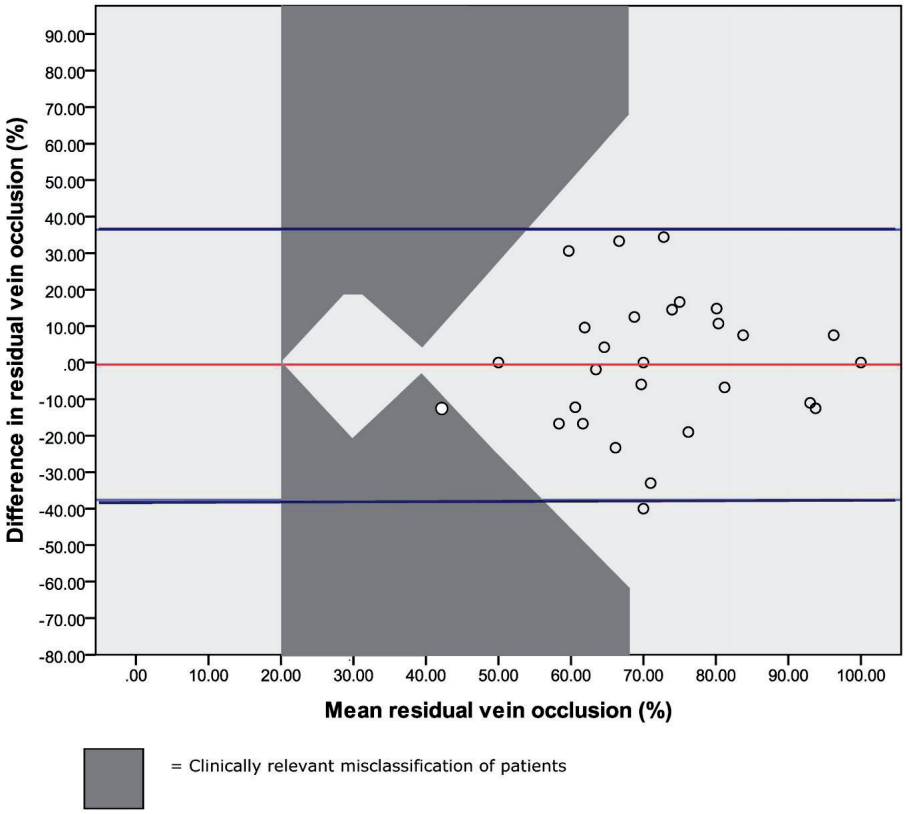

Figure 4 .Bland–Altman plot for occlusion percentage of residual vein occlusion. Red line: mean difference in thrombus diameter. Blue lines: standard deviation.

by 0.6%. One case (3.6%) differed by > 2 SDs from the mean. The 95th percentile for the difference in occlusion assessments between the two observers was 33.9%.

Table 3 shows the number of patients and corresponding percentages for the cut-off points for the occlusion percentages between the observers. Thrombus occlusion differed between the observers by < 10% in 35% of patients measured, but the difference was < 25% in 82% of all studies.

We also examined whether imperfections in the interobserver reliability would have clinical consequences. Of the 28 patients who were classified as having residual thrombosis by both observers, one patient (3.6%) would be differently classified, according to the definition of the presence of residual venous thrombosis in the case of an occlusion of ≥ 40%, by the two observers because of interobserver variability.

Interobserver agreement on measurement of the distance between the proximal terminus of residual thrombosis and the SFJ

Of the 28 patients in whom both observers agreed on the presence of residual thrombosis (thrombus diameter of ≥ 2 mm), the distance between the proximal terminus of the residual thrombosis and the SFJ was measured in 23 patients by observer 1 and in 25 patients by observer 2. The mean distances between the proximal terminus and the SFJ were 17.63 cm (SD 14.46) for observer 1 and 19.92 cm (SD 15.2) for observer 2. For the interobserver agreement, we included the patients in whom both observers reported on the measurements of the distance between the proximal terminus of the residual thrombosis and the SFJ. In 20 of the 28 patients, both reviewers reported measurements for the distance between the proximal terminus of the residual thrombosis and the SFJ. The Pearson coefficient of the correlation between distances in assessments of both observers was 0.984 (P = 0.000), indicating an excellent correlation between the measurements. Figure 5 shows the Bland-Altman plot with the mean thrombus diameter on the X-axis and the differences in measurements for the distance between the proximal terminus of the residual thrombosis and the SFJ on the Y-axis. There was no difference between the measurements (mean = 0 cm), and the SD was 4.9 cm. Two (10%) of the

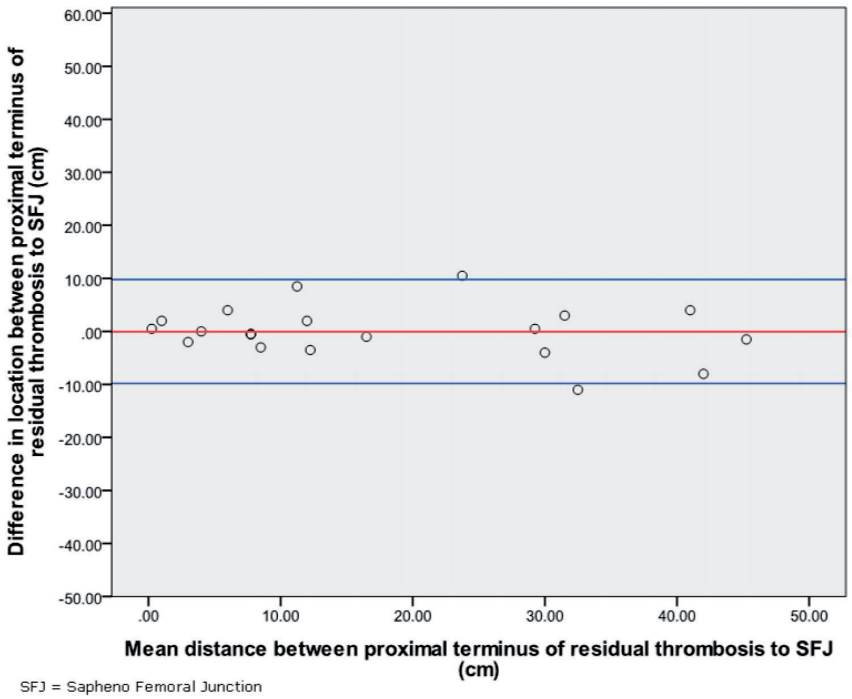

Figure 5. Bland–Altman plot for the distance (in cm) from the saphenofemoral junction (SFJ). Red line: mean difference in thrombus diameter. Blue lines: standard deviation.

patients were outside the ± 2 SD area of the mean. The 95th percentile of the measurements was 10.4 cm. Table 3 shows the number of patients and corresponding percentages for the cut-off points of differences in measurements between the two observers. In 50% of the patients, the difference in distance between the proximal terminus of the residual thrombosis and the SFJ was ≤ 2 cm, and 90% of the patients had a difference of 10 cm or less.

DISCUSSION

We assessed the interobserver reliability of residual thrombosis measurement and examined the clinical implications of imperfect interobserver reliability. Our study showed high interobserver reliability for the determination and measurement of residual thrombosis (i.e. thrombus diameter of ≥ 2 mm), the interobserver reliability for the determination of residual occlusion was fair, but this seemed to have limited clinical implications. The interobserver reliability for determination of residual venous occlusion was fair according to the Pearson correlation in patients in whom both observers agreed on the presence of residual thrombosis (i.e. thrombus diameter of ≥ 2 mm), with a high variance in percentages; however, according to the Bland–Altman plot, this had minimal clinical implications. The interobserver reliability for the measurements of the distance between the residual thrombosis and SFJ was high according to Pearson correlation, but in the Bland–Altman plot 10% of the patients were outside 2 SDs, and the variance in measurements was high.

Linkins et al. explored the interobserver reliability of residual vein diameter measurement in 60 patients who had a proximal DVT diagnosed within 3 months, or who had previously documented non-compressibility on ultrasonography at least 3 months post-diagnosis. The interobserver reliability of measurement of the residual thrombosis was moderate, with a mean difference of 2.2 mm between observers and an upper limit error of 8 mm. The interobserver reliability was very good with one observer reading the same scan on two separate occasions (r^2 = 96%), but poor with evaluation of ultrasonography films taken by two separate examiners (r^2 = 12%).[14]

This study differed from our study in that we systematically examined patients between 5.5 months and 7 months after their thrombosis, whereas the patients enrolled in the study of Linkins et al. were enrolled 2 weeks up to 4 years after their acute DVT episode. This variability in time could be relevant, as patients would have a higher chance of having a residual thrombosis 2 weeks after their event than after 4 years. Furthermore, our cohort better reflects clinical practice, because, in clinical practice, patients would also be evaluated after a fixed time point (e.g. after the cessation of anticoagulation).

Our study showed a lower interobserver reliability than a recent study performed by Hassen et al.[15] In this study, the interobserver reliability of thrombus measurement was assessed directly after the acute DVT episode. This study showed a high interobserver reliability ($r^2 = 0.91$) for the measurement of thrombosis diameter in the acute DVT setting. However, the interpretation of the data in both studies was based on the Pearson correlation coefficient. The Pearson correlation coefficient has been shown to have limitations when used as an interpretation of interobserver reliability. The use of a Bland–Altman plot has been suggested.[16] A Bland–Altman plot is more informative than the Pearson correlation, as it gives information about the difference between thrombus diameter measurements in relation to the average diameter. The Bland–Altman plot is interpreted by looking at the area of ± 2 SD from the mean; however, this interpretation is a statistical interpretation, and does not tell us anything about the clinical implications of the interobserver reliability. In this study, we have developed a method in which we use the Bland–Altman plot to show the clinical implications of interobserver variability.

Besides the fact that this article is the first to report on the clinical implications of interobserver reliability in the measurement of residual thrombosis, the study has other strengths. It is the first on the interobserver reliability of residual occlusion percentage measurement. Residual vein occlusion of ≥ 40% has been mentioned in several studies as the definition for the presence of residual thrombosis; however, no studies have been performed to assess interobserver reliability. Furthermore, the patients in the study were consecutively enrolled without bias, and all data were collected in a systematic manner.

Our study has several limitations. First, we did not collect the thrombosis diameter and residual venous occlusion values for all patients, but only for those in whom one or both observers determined the presence of residual thrombosis (i.e. thrombus diameter of ≥ 2 mm during compression). However, when we examined the clinical implications of the interobserver reliability in measuring residual thrombosis, we showed both the worse case scenario and the best case scenario. Furthermore, our results should be interpreted with caution because of the limited sample size.

This study is the first to systematically assess the interobserver reliability of measurements in patients after a fixed period of time after their acute thrombosis. Our results suggest that the interobserver reliability of baseline ultrasonography would not be a limitation in this setting; however, it is possible, but unlikely, that the interobserver reliability might be a limitation in patients with suspected recurrent DVT. In our study, we conservatively showed that, in the worse case scenario, 4% of patients would be clinically misclassified because of interobserver variability. This suggests that the interobserver reliability in the measurement of residual thrombosis has minimal clinical consequences for the measurement and determination of residual thrombosis. Our results have potential clinical implications for the use of baseline imaging for both diagnostic and prognostic management after a DVT.

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