Post-thrombotic syndrome is an independent determinant of health-related quality of life following both first proximal and distal deep vein thrombosis

Post-thrombotic syndrome (PTS) is a common complication of deep vein thrombosis (DVT), affecting between 20 and 50%.[1] DVT and PTS have been demonstrated to adversely impact on disease-specific and generic measures of health-related quality of life (QOL).[2,3] We sought to establish determinants of QOL, and the impact of PTS in our local population with a first DVT.

The disease-specific measure of QOL used in this study was the VEINES-QOL survey. It was developed for use in chronic venous disorders[4] and has been evaluated specifically in patients with DVT.[3,5,6] Professor Kahn kindly gave permission for use of the VEINES-QOL survey and provided the scoring tool.[4] The generic measure of QOL used was the short form (SF)-36 health survey. A licence for its use was purchased from Quality Metric Inc. (Lincoln, USA). Responses were entered into an online computerized scoring tool (Smart Measurement System, Quality Metric Inc, Lincoln, USA) which provided two summary scores: the physical component summary (PCS) score and mental component summary (MCS) score.

PTS was diagnosed using the Villalta scale as previously described,[7,8] with a Villalta scale of 5 or more at either follow-up assessment indicating the presence of PTS. The maximum score at either assessment was utilized for grading severity, with a maximum score of 5-9 indicating mild PTS and maximum score of 10 or over indicating moderate/severe PTS.

Participants were recruited to the Camberwell DVT outcomes study as previously described.[7] Participants with proximal DVT (involving popliteal vein or above) continued anticoagulation for six months and those with isolated distal DVT for three months. QOL surveys were completed at recruitment, six weeks (T2) and six months (T3) following completion of anticoagulation (or at 6 and 12 months following DVT diagnosis in those on extended anticoagulation).

Linear regressions were used to model QOL at baseline and PTS from three months. A mixed linear regression was used to model the effect of PTS and other clinical and demographic variables on the longitudinal change of QOL across the three assessment times. All the mixed regressions (univariate and multivariate) adjusted for the time effect (the multi-level approach takes into account the cluster effect of time within cases). Multivariate models allow the models to adjust for the effects of possible confounders and to evaluate interactions. Our multivariate models were fitted in a stepwise manner, adjusting for those variables that showed significance below the 0.25 threshold univariately. Statistical significance in all final models was ascribed at the 5% level. All statistical analyses were performed in SPSS v18.0 (IBM, New York, USA) and Stata v.12. The study was approved by the Brent Research Ethics Committee (08/H0717/083) and the Research and Development department at King's College Hospital NHS Foundation Trust. All patients gave written informed consent prior to study entry.

One hundred and thirty-three participants with DVT were recruited with 122 returning to at least one follow-up assessment as previously described.[7] QOL was measured with the SF-36 and VEINES-QOL surveys in 116 and 122 patients, respectively, at baseline, 122 participants at T2 and 114 participants at T3. PTS developed in 51.6% by end of study, with 31.1% developing mild and 20.5% moderate/severe PTS.

Table 1. Base-line characteristics and longitudinal changes in quality of life (QOL) by post-thrombotic syndrome (PTS) severity.

Characteristic	PTS status		
	N PTS	Mild PTS	Moderate/ severe PTS
N (%)	59 (48.4)	38 (31.1)	25 (20.5)
Mean age (SD)	41 (11)	54 (15)	53 (16)
Males (%)	32 (54)	24 (63)	8 (32)
Mean BMI, kg/m^2 (SD)	28 (5)	32 (8)	29 (6)
Ethnicity, n (%)			
Caucasian	34 (58)	24 (63)	12 (48)
African-Caribbean	19 (32)	10 (26)	12 (48)
Mixed/Other	6 (10)	4 (11)	1 (4)
Provoked DVT, n (%)	37 (63)	19 (50)	14 (56)
Proximal DVT, n (%)	25 (42)	24 (63)	13 (52)
Charlson Index, n (%)			
Index=0	53 (90)	27 (73)	14 (56)
Index>0	6 (10)	10 (27)	11 (44)
Generic QOL (SF – 36)#, mean (SD)			
PCS baseline	n= 56, 49 (11)	n=35, 45 (11)	n= 25, 45 (12)
PCS T2	n=59, 53 (8)	n=38, 45 (11)	n=25, 38 (11)
PCS T3	n=55, 53 (8)	n=36, 48 (10)	n=22, 37 (10)
MCS baseline	n=56, 48 (12)	n=35, 50 (10)	n=25, 42 (14)
MCS T2	n=59, 50 (10)	n=38, 51 (10)	n=25, 43 (14)
MCS T3	n=55, 51 (9)	n=36, 51 (9)	n=22, 44 (16)
Venous disease-specific QOL#, mean (SD)			
VEINES-Sym baseline	n=59, 47 (9)	n=38, 44 (9)	n=25, 38 (9)
VEINES-Sym T2	n=59, 58 (4)	n=38, 52 (8)	n=23, 41 (10)
VEINES-Sym T3	n=55, 58 (5)	n=37, 54 (6)	n=22, 43 (9)
VEINES- QOL baseline	n=59, 45 (8)	n=38, 44 (9)	n=25, 37 (9)
VEINES- QOL T2 (SD)	n=59, 58 (3)	n=38, 52 (7)	n=23, 42 (10)
VEINES- QOL T3 (SD)	n=55, 58 (5)	n=37, 55 (6)	n=22, 44 (10)

#For all parameters, lower scores indicate poorer QOL (quality of life). PTS: post-thrombotic syndrome; SD: standard deviation; BMI: body mass index; SF-36: short-Form 36; T2: six weeks post end of anticoagulation; T3: six months post end of anticoagulation.

Base-line characteristics of the study population and longitudinal changes in QOL are summarized in Table 1. Progressive severity of PTS was associated with attenuation in improvement from base-line QOL scores (Table 1). On linear regression, at baseline, generic QOL scores were significantly associated with gender and Charlson index. On average, female patients had significantly lower PCS (mean -5.6, 95%CI: -9.5 to -1.7; P=0.01) and MCS (-5.2, 95%CI: -9.5 to -0.97; P=0.02). PCS was, on average, significantly lower for those with Charlson index of 1 or over (-9.8, 95%CI: -14.4 to -5.2; P<0.0001). Only a borderline significant association of VEINES QOL with Charlson index of 1 or over was observed (-3.8; 95%CI: -7.9 to 0.23; P=0.06).

Determinants of QOL, throughout follow up, are shown in Table 2. All interactions with proximity of DVT were found to be non-significant (P>0.10), implying that the results hold for proximal and distal DVT.

At presentation with DVT, SF-36 PCS scores were below reported population norms for the United Kingdom; those who did not develop PTS recovered generic SF-36 PCS scores to within published population norms by end of follow up (mean PCS in those without longstanding illness 53.6 +/-5.9).[9] However, even mild PTS

Table 2. Multivariate mixed regressions for difference in quality of life scores throughout follow up (QOL).

QOL measure	Variable	Coefficient#	95% CI	P
SF-36 PCS	Gender (F *vs.* M)	-5.2	-8 to -2	0.001
	Charlson Index (≥1 *vs.* 0)	-8	-12 to -4.5	<0.001
	PTS			0.01
	Mild *vs.* no PTS	-5	-9 to -1.5	0.01
	Moderate/severe *vs.* no PTS	-6	-10 to -1.0	0.02
SF-36 MCS	Gender (F *vs.* M)	-4.7	-8 to -1.1	0.01
	PTS			0.54
	Mild *vs.* no PTS	-2.3	-7 to 1.9	0.29
	Moderate/severe *vs.* no PTS	-1.7	-7 to 3.5	0.53
VEINES-Sym	Gender (F *vs.* M)	-2.4	-5 to -0.24	0.03
	Charlson Index (≥1 *vs.* 0)	-2.8	-6 to -0.1	0.04
	PTS			<0.001
	Mild *vs.* no PTS	-8	-11 to -5	<0.001
	Moderate/severe *vs.* no PTS	-10	-13 to -7	<0.001
VEINES-QOL	Age	0.10	0.01 to 0.18	0.02
	Gender (F *vs.*M)	-3	-5 to -0.3	0.03
	Charlson Index (≥1 *vs.* 0)	-4	-6 to -0.8	0.01
	PTS			<0.001
	Mild *vs.* no PTS	-7	-10 to -4	<0.001
	Moderate/severe *vs.*no PTS	-8	-12 to -5	<0.001

The multivariate models were fitted in a stepwise manner, adjusting for those variables that showed significance below the 0.25 threshold univariately. All regressions are adjusted for time. #Mean effect on score, a negative change indicates a deterioration in quality of life (QOL). CI: confidence interval; SF-36: Short-Form 36; PCS: physical component score; MCS: mental component score; F: female; M: male; PTS: post-thrombotic syndrome.

resulted in end of study SF-36 PCS scores significantly below published population norms. Therefore, prevention of PTS is paramount to restore QOL following DVT.

In keeping with previous studies, female gender and comorbid disease were associated with poorer generic QOL scores.[9] However, in contrast to previous reports,[3,5] proximity of DVT was not found to be a significant determinant of physical QOL. Additionally, the disease-specific VEINES-QOL tool was less specific to PTS than previously reported;[3] with age, gender and Charlson index also influencing QOL in this study. It is important to note that our study is limited by the number of participants and short duration of follow up, and thus these findings require confirmation in further studies.

PTS was the only potentially modifiable factor significantly associated with end of study QOL scores, irrespective of DVT location. Recent guidance advises against routine imaging and diagnosis of distal DVT due to the low risk of extension and embolization; the risk of bleeding with anticoagulation is, therefore, felt to outweigh any benefit.[10,11] Distal DVT accounts for 40-50% of all DVT and is associated with PTS, albeit with a lower incidence compared to proximal DVT (~40-45% *vs.* ~50-60% respectively).[3,7] Given that the two principal strategies for PTS prevention following proximal DVT are adequate anticoagulation[12,13] and daily wear of below knee graduated compression stockings,[10] not diagnosing (and therefore not treating) distal DVT has the potential to increase the already large burden of chronic venous disease on society.[14,15] Previous studies have shown PTS is associated with a greater adverse impact on QOL compared to other chronic venous disease and is comparable to chronic medical conditions such as diabetes and congestive heart failure.[2,3] Thus our finding that PTS is a strong determinant of QOL in DVT patients, irrespective of DVT location, is highly relevant in the light of current guidance. We suggest further research is required to establish long-term outcomes, such as PTS following distal DVT, and particularly following strategies in which anticoagulation is withheld in the absence of proximal extension.

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