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Comparison of quality of life measurements: EQ-5D-5L versus disease/treatment-specific measures in pulmonary embolism and deep vein thrombosis

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Abstract

Introduction There is a lack of performance comparisons of the generic quality of life tool EQ-5D-5L against disease- and treatment-specific measures in venous thromboembolism (VTE). The aim of this study was to compare EQ-5D-5L against the pulmonary embolism (PE)-specific PEmb-QoL and the deep vein thrombosis (DVT)-specific VEINES-QOL/Sym, and PACT-Q2 (treatment-specific) questionnaires in five language settings.

Methods PREFER in VTE was a non-interventional disease registry conducted between 2013 and 2014 in primary and secondary care across seven European countries with five languages, including English, French, German, Italian and Spanish. Consecutive patients with acute PE/DVT were enrolled and followed over 12 months. Only patients who completed all three questionnaires at baseline were included in the study sample. The psychometric properties examined included acceptability (missing, ceiling and floor effects), validity (convergent and known-groups validity), and responsiveness. Known groups validity and responsiveness were assessed using both effect size (Cohen's *d*) and relative efficiency (*F*-statistic). All analyses were conducted in each language version and the total sample across all languages.

Results A total of 1054 PE and 1537 DVT patients were included. 14% of PE and 10% of DVT patients had the maximum EQ-5D-5L index score. EQ-5D-5L was low to moderately correlated with other measures ($r < 0.5$). EQ-5D-5L was associated with larger effect size/relative efficiency in most of known group comparisons in both VTE groups. Similar results were observed for responsiveness. EQ-5D-5L performed relatively better in French, Italian and Spanish language versions.

Conclusion Overall EQ-5D-5L is comparable to PEmb-QoL, VEINES-QOL/Sym and PACT-Q2 in terms of acceptability, validity and responsiveness in both PE and DVT populations in English, French, German, Italian and Spanish language version. Nevertheless, it should be noted that each measure is designed to capture different aspects of health-related quality of life.

Keywords EQ-5D-5L · Pulmonary embolism · Deep vein thrombosis · Venous thromboembolism · PEmb-QoL · VEINS-QOL/Sym · PACT-Q2

Introduction

EQ-5D [1] is a generic health-related quality of life (HRQoL) measurement. It was developed in 1990 by the EuroQol group (http://www.euroqol.org). It is a widely used instrument and commonly employed in clinical trials, observation studies, and population health surveys. EQ-5D is also the dominant utility/preference-based measure for health technology assessment (HTA) in several major healthcare systems, and its use to assess health outcomes is growing.

The EQ-5D comprises of two parts: the descriptive system and a visual analogue scale (VAS). The descriptive system consists of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression), and the original 3-level EQ-5D (EQ-5D-3L) has three levels of response ("no problem", "some/moderate problem", and "extreme problem") for each dimension. The main criticism of EQ-5D-3L is a lack

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of descriptive richness [2, 3] and suffering from a ceiling effect [4]. To tackle these potential issues, a 5-level EQ-5D (EQ-5D-5L) [5] has been developed where the descriptive levels of each item has increased to five: ''no problems'', ''slight problems'', ''moderate problems'', and ''severe problems'' for all five items, and ''unable to do'' for mobility, self-care, and usual activities or ''extreme problems'' for pain/discomfort and anxiety/depression. In some studies, the EQ-5D-5L has been demonstrated to have better sensitivity, discriminative power and fewer ceiling effects than the EQ-5D-3L [6–8].

Given the expected improvement over the original 3L version, the use of the EQ-5D-5L has grown rapidly. Several studies have been published to report the psychometric property of EQ-5D-5L in general [9, 10] and patient populations including cancer [7], hepatitis [11], stroke [12, 13], Parkinson's disease [14], and HIV/AIDS [15]. As yet the use of EQ-5D-5L in pulmonary embolism (PE) and deep vein thrombosis (DVT) populations has not been validated. Furthermore, there is a lack of comparison of performance of EQ-5D-5L against disease specific measures.

This study aimed to compare the measurement properties between EQ-5D-5L and PE and DVT disease-specific questionnaires (PEmb-QoL and VEINES-QOL/Sym) and the treatment-specific questionnaire (PACT-Q2) in both PE and DVT populations. As a result of an international study, the questionnaires were administrated in five different languages. The comparisons were made in each of the five language settings individually and the pooled data across all languages. The psychometric properties examined included acceptability (missing, ceiling and floor effects), validity (convergent and known-groups validity), and responsiveness.

Methods

Patients

The data is based on the PREFER in VTE registry. It was a prospective, observational, multicenter study conducted in seven European countries including Austria, France, Germany, Italy, Spain, Switzerland, and the UK. The aim of the PREFER study was to assess the characteristics and the management of patients with VTE, the use of healthcare resources, and to provide data on estimating the costs for 12 months treatment following a first-time and/or recurrent VTE diagnosed in hospitals or in specialized or primary care centers [16]. Patients were eligible to be enrolled into the registry if they were at least 18 years old, had a symptomatic, objectively confirmed first time or recurrent acute VTE defined as either distal or proximal deep vein thrombosis (DVT), pulmonary embolism (PE) or both. After the baseline visit at the time of the acute VTE event, further follow-up documentations occurred at 1, 3, 6 and 12 months. Overall, 381 centers participated, enrolling 3455 patients during an observational period of 1 year (PE: 1399 and DVT: 2056) [17]. Of note, Austria, Switzerland, and Germany were combined into one pre-specified region label (DACH). The DACH countries were grouped in a cluster as the patient population, practice patterns and healthcare systems were assumed to be similar.

Instruments and measures

EQ-5D-5L

As described above, the EQ-5D-5L [5] is a self-report questionnaire with five items and five levels for each item (the descriptive system). Respondents choose one level for each item to describe their health status on the day of interview. Responses to the five EQ-5D items define a health state for which an index score can be generated to indicate its value to the general public. For this study, the UK value set has been applied to generate the index score [18]. The index score is anchored by 0 (death) and 1 (full health), with higher scores corresponding to higher utility (scores ranging from − 0.281 to 1). The second component of the EQ-5D is a visual analogue scale (VAS) which indicates the respondent's general health status on a scale from 0 (worst imaginable health status) to 100 (best imaginable health status). Comparing with the 3L version, the EQ-5D VAS in the 5L version remains the same but with an improved user-friendly design.

Pulmonary embolism quality of life (PEmb-QoL) questionnaire

PEmb-QoL is a disease-specific questionnaire, developed to assess QoL in patients with PE [19]. It covers six domains: frequency of complaints (eight items), activities of daily life (ADL) limitations (13 items), work-related problems (four items), social limitations (one item), intensity of complaints (two items) and emotional complaints (ten items). PEmb-QoL also contains two additional descriptive items: the time of the day with the most intense lung symptoms and the comparison of lung condition between new and 1 year ago. Respondents are required to

answer on two-point to six-point Likert response scales of intensity, frequency, or agreement, based on their experience during the past 4 weeks (except two descriptive items). Scores for all dimensions are calculated by the sum of the scores for each item of the dimension divided by the number of the items (one score for each dimension). Higher scores indicate worse outcome—more complaints/limitations (score for each dimension ranging from 1 to 2–6).

VEINES-QOL/Sym

VEINES-QOL/Sym, a disease-specific questionnaire containing a 26-item measures the impact of deep venous thrombosis on symptoms and quality of life from the patient's perspective [20]. The items cover symptoms (ten items), limitations in daily activities (nine items), time of day of greatest intensity (one item), change over the past year (one item), and psychological impact (five items). Respondents are rated on two-point to seven-point Likert response scales of intensity, frequency, or agreement. The time frame for questions about symptoms, daily limitations, and psychological impact covers the previous 4 weeks. Two summary scores can be computed. The VEINES-QOL summary score (25 items) provides an estimate of the overall impact of deep venous thrombosis on the patient's quality of life. The VEINES-Sym summary score (ten items) measures symptom severity. Higher summary scores equate to better outcomes. To calculate both summary scores, raw scores are first transformed to *z*-score equivalents (mean 0; standard deviation 1), which are then transformed to *T*-scores (mean 50; standard deviation 10) to give an easily understood range of scores (scores ranging from 19 to 69*).

Perception of anti-coagulant treatment questionnaire (PACT-Q)

PACT-Q is a treatment-specific questionnaire, developed to investigate the burden of disease in patients with DVT, PE or atrial fibrillation (AF), with specific focus on patients' satisfaction with anticoagulant treatment and treatment convenience [21]. The PACT-Q consists of two parts: PACT-Q1 and -Q2. PACT-Q1 focuses on the patient's expectation over their anticoagulant treatment (seven items) and this part should be administered before treatment initiation; PACT-Q2, composed of two dimensions, the convenience of use of the treatment (13 items) and satisfaction with the anticoagulant treatment (seven items) as perceived by the patient, is to be administered to patients once the treatment is ongoing. The current study concerns PACT-Q2 only. All items are answered on a 5-point Likert scale. Two summary scores (treatment convenience and satisfaction) are calculated on a 0–100 scale, with a higher score indicating better outcomes.

Statistical analysis

In terms of descriptive statistics, for continuous variables, means and standard deviations (SD) were presented, while frequencies and proportions from categorical variables were shown. For each questionnaire, the distributions of scores, the mean (SD), median, and the percentage of respondents with the minimum/maximum scores (indicating flooring and ceiling effects) were presented. The criteria of acceptability of each questionnaire included: $< 5\%$ missing data for summary scores, even distribution of endorsement frequencies across response categories, and $< 10\%$ floor and ceiling effects for summary scores.

Convergent validity

Convergent construct validity was investigated by examining the correlation, using Pearson's correlation coefficient (r), between the EQ-5D-5L and the PEmb-QoL, VEINES-QOL/Sym and PACT-Q2 scores, respectively. Convergent usually refers to correlation with other measures of same or similar constructs. Thus, the tested hypothesis was that there would be a low to median correlation ($r < 0.5$) between generic measures and the disease/treatmentspecific measures.

Known-group validity

Known-groups validity examined a hypothesis that patients in better health status have higher scores than those in worse health status. Thus, the study sample was categorized into subgroups in better and worse health status according to patients' comorbidity (≤ 1 comorbidity condition vs. > 1 comorbidity conditions), provoked, distal vs. proximal (for DVT patients only) at the baseline, and dead (yes vs. no) during the follow-up period. The comorbidity included the following diseases: active cancer, congestive heart failure, vascular disease, dyslipidemia, diabetes, chronic venous insufficiency, renal disease, liver disease, chronic respiratory disease, arthritis, bone fracture/soft tissue trauma, lower extremity

paralysis, thrombophilia and cardiovascular disease. Provoked PE/DVT was defined as having prolonged immobilization, > 5 days in bed, or history of major surgery or trauma. The relative efficiency (RE) statistic and effect size (Cohen's d) were applied to evaluate the performance (the sensitivity to detect differences) in each known group. The RE statistic is defined as the ratio of F-statistics in the analysis of variance (ANOVA) tests of the differences in scores between known groups [22, 23]. To calculate the RE value of comparator score, the F statistic of the EQ-5D-5L index was used as the reference (RE = 1) in each pair of known groups. The higher F-statistic values indicate to be more efficient or discriminative than its comparator. The effect size was calculated using the difference in mean scores divided by the pooled SD [23, 24]. The threshold values of 0.2, 0.5, and 0.8 to define small, moderate, or large effect size, respectively.

Responsiveness

Responsiveness (sensitivity to change) was also assessed by RE and effect size. Responsiveness typically refers to the ability to detect clinically important change over time. Patients who reported experiencing clinical events during 1-month follow-up were expected to have lower scores comparing to those who did not experience clinical events. Clinical event was defined as bleeding, recurrence of DVT/PE, myocardial infarction, stroke, systemic embolic events, post-thrombotic syndrome, and cardiovascular (CV) events.

The hypothesis of the study is that EQ-5D-5L is comparable to other disease-specific/treatment-specific measures, in terms of all examined psychrometric properties. Apart from analyzing the total sample, the analysis of each individual language was conducted to account for potential differences in between instructions in each language setting. As the data were collected in various countries with five languages, English (the UK), French (France), German (DACH), Italian (Italy), and Spanish (Spain), five separate analyses were performed. Thus, the study provides the required evidence to support the validation of EQ-5D-5L in PE/DVT in each language setting.

Note that since PEmb-QoL generates six domain scores with the range of values varying from 1–2 to 1–6 for each domain. One might argue that these domain scores of PEmb-QoL has no cardinal property. Thus, to facilitate the comparison between PEmb-QoL and EQ-5D-5L, two single summary scores of PEmb-QoL have been calculated based on equal weight from each domain and from each item, respectively. Then, these summary

Table 1 Patient characteristics at baseline

Characteristics	Total		France		DACH		Italy		Spain		UK	
	PE	DVT	PE	DVT	PE	DVT	PE	DVT	PE	DVT	PE	DVT
	$n = 1054$	$n = 1537$	$n = 296$	$n = 172$	$n = 170$	$n = 482$	$n = 252$	$n = 433$	$n = 219$	$n = 151$	$n = 117$	$n = 299$
Age, mean (SD)	61.9 (17.2)	59.6 (16.7)	60.7 (17.3)	57.7 (16.4)	58.2 (16.8)	56.9 (16.2)	66.2 (17.3)	64.3 (16.2)	63.3 (17.3)	59.5 (18.2)	59.0 (14.3)	58.3 (16.1)
Male (*n*)	53.89% (568)	53.9% (829)	53.4% (158)	47.7% (82)	58.2% (99)	53.9% (260)	47.62% (120)	50.1% (217)	55.3% (121)	59.6% (90)	59.8% (70)	60.2% (180)
Education (*n*)												
Primary school	31.95% (324)	25.08% (372)	18.1% (49)	18.2% (31)	27.2% (44)	21.8% (99)	50% (125)	40.6% (169)	49.3% (106)	45.6% (67)	0% (0)	2% (6)
Secondary school	43.79% (444)	52.06% (772)	49% (132)	52% (88)	46% (74)	53% (241)	38.8% (97)	45.9% (191)	33% (70)	35% (51)	61% (71)	68% (201)
Above secondary	24.26% (246)	22.86% (339)	33.2% (90)	30% (51)	27.2% (44)	25.1% (114)	11.2% (28)	13.5% (56)	18.1% (39)	19.7% (29)	38.8% (45)	30.1% (89)
Provoked (*n*)	27.1% (286)	27.3% (419)	24% (70)	26% (44)	24% (41)	25% (122)	37.3% (94)	32.3% (140)	25% (54)	28% (42)	23% (27)	24% (71)
Proximal (*n*)	–	71.6% (1100)	–	48.8% (84)	–	65.4% (315)	–	77.1% (334)	–	85.4% (129)	–	79.6% (238)
Comorbidity > 1, (*n*)	50.9% (536)	48.4% (744)	45.6% (135)	45.9% (79)	45.9% (78)	39.2% (189)	64.7% (163)	60.7% (263)	49.3% (108)	55% (83)	44.4% (52)	43.5% (130)
Death (*n*)	6.2% (60)	7% (94)	4.3% (12)	7.2% (11)	0.7% (1)	2.5% (11)	12.7% (30)	14.5% (54)	7.4% (15)	7.7% (11)	2.2% (2)	3% (7)

scores are transformed to a 0–100 scale, with a higher score indicting better outcomes.

All statistical analyses were performed using STATA (release 12; Stata Corp, College Station, TX, USA) statistical software, with $p < 0.05$ being considered significant.

Results

Study patient characteristics

In total, 3455 patients were recruited in the PREFER registry, 1399 for PE and 2056 for DVT. The study sample was limited to patients who completed all EQ-5D-5L (both the descriptive system and VAS), PEmb-QoL (for PE) or VEINES-QOL/Sym (for DVT), and PACT-Q2 measures, and this resulted in the study sample of 1054 and 1537 (complete cases) for PE and DVT, respectively. The analysis sample for each language were French 296/172, German 170/482, Italian 252/433, Spanish 219/151 and English 117/299 for PE/DVT. The demographic characteristics of participants in each language setting are described in Table 1. Overall, the average age was 62.0 (SD: 17.2) and 59.6 (16.7) years for PE and DVT, respectively, and the proportion of male participants were 53.9% in both populations. The percentage of provoked was around 27% in both PE and DVT and in patients with DVT 71.6% of the clots were located proximally. The proportion of patients with greater than one comorbidity was 50.9% and 48.4%, respectively. The proportion of deaths occurring during the study was 6.2% and 7.0%, respectively. Of note, in the following text, only the result tables based on the total sample are presented. The country-specific result tables can be found in "Appendix" section.

Ceiling/floor effect and missing

The mean and median, of summary scores of each measure in the total sample are presented in Table 2. The distribution of each summary score of each measure in the total sample are illustrated in Figs. 1 and 2. As shown in the figure, EQ-5D-5L index score and convenience score of PACT-Q2 in both populations had skewed distributions with a large number of patients reporting higher scores. Note that six domain scores of PEmb-QoL were presented in box plot due to its coarse scale. The ceiling effect of EQ-5D-5L index score was 13.8% and 9.7% in the total PE and DVT population, respectively (Table 2). The ceiling effect of EQ-5D-5L index score (> 10%) was observed in all language versions, except the Italian version for PE population; while in DVT, the ceiling effect was observed in French and German languages only (Table 7 in "Appendix" section). The ceiling effect was also observed on the convenience score of PACT-Q2 in the total sample as 8.1% in PE and 9.0% in DVT. This ceiling effect of the convenience score of PACT-Q2 was also observed in German and English settings for PE, as well as French and German for DVT (Table 7 in "Appendix" section). Several domain scores of PEmb-QoL demonstrated high proportions of patients with maximum score, such as domain of work-related problems and social limitations in the total sample and each language version. Similarly, a high proportion of patients with minimum score was observed in several domains of PEmb-QoL. However, this was mainly due to the limited level of response. For instance, there is only two response level (yes/no) in the questions of work-related problem. More details can be found in the "Discussion" section. No floor effect (> 10%) was observed in EQ-5D-5L index/VAS and PACT-Q2 measures in the total sample and each language version. In terms of missing observations, a higher proportion of missing observations was observed in PACT-Q2 in the total and each language version, 9.7–29.4% in PE and 13.6–33.3% in DVT, whereas EQ-5D-5L had the lowest missing observations rate, 0.7–3.7% and 0.8–3.9% in PE and DVT, respectively.

Convergent validity

Table 3 and Table 8 in "Appendix" section demonstrates the correlations between each measure (convergent validity) in the total sample and each language version. As expected, EQ-5D-5L index score was low to moderately correlated with scores of other measures ($r < 0.5$). The exceptions were observed between the index score and activities of daily living (ADL) limitation domain (PEmb-QoL) in the French, Italian and English versions, $r = 0.509$–0.629, and between the index score and VEINES-QOL score (0.613) in the English version. Similar correlations were observed for EQ-5D VAS score.

Known-group validity

In the PE study population, EQ-5D-5L index/VAS score was associated with larger effect size/relative efficiency in most of the known-group comparisons compared to PEmb-QoL and PACT-Q2, as shown in Table 4 for the total sample and Table 9 in "Appendix" section for each language version. The exceptions were

Table 2 Acceptability—scores of each measure at baseline

Disease	Measures	Scores	n	Mean (SD)	Median	Min	Max	% of patients on "floor"	% of patients at "ceiling"	% Missing[a]
PE	EQ-5D-5L	Index score	1054	0.717 (0.260)	0.777	− 0.281	1	0.47	13.76	2.36
		Visual analogue score (VAS)		60.12 (20.64)	60	0	100	0.47	1.90	
	PEmb-QoL	Frequency of complaints		2.27 (1.03)	2	1	5	9.49	1.33	5.79
		ADL limitations		2.00 (0.66)	2	1	3	10.44	7.78	
		Work related problems		1.62 (0.44)	2	1	2	29.13	50.38	
		Social limitations		2.55 (1.37)	2	1	5	32.92	9.68	
		Intensity of complaints		3.24 (1.40)	3	1	6	11.57	3.98	
		Emotional complaints		2.57 (1.21)	2.3	1	6	9.39	0.38	
		EWBD		56.91 (24.27)	54.98	1.33	100	0.09	1.80	
		EWBI		58.60 (23.14)	58	1.08	100	0.09	1.80	
	PACT-Q2	Convenience		80.84 (17.51)	86.54	3.85	100	0.09	8.06	19.44
		Treatment satisfaction		65.54 (14.87)	64.29	0	100	0.09	1.71	
DVT	EQ-5D-5L	Index score	1537	0.720 (0.242)	0.788	− 0.281	1	0.20	9.69	2.87
		Visual analogue score (VAS)		64.87 (20.06)	70	0	100	0.46	2.47	
	VEINES-QOL/Sym	VEINES-QOL		49.24 (9.75)	49.84	19.18	68.8	–	–	4.47
		VEINES-Sym		49.28 (9.72)	49.78	22.15	65.71	–	–	
	PACT-Q2	Convenience		82.33 (15.86)	86.54	5.77	100	0.07	9.04	18.24
		Treatment satisfaction		65.40 (15.37)	67.86	0	100	0.33	0.85	

EWBD equal weight based on each dimension, *EWBI* equal weight based on each item

[a]EQ-5D-5L: missing any of six items (including EQ-VAS); VEINES-QOL/Sym: more than 12 items (out of 25) missing; PEmb-QoL: 50% missing at any of six dimensions; PACT-Q2: more than 7 + 5 items missing

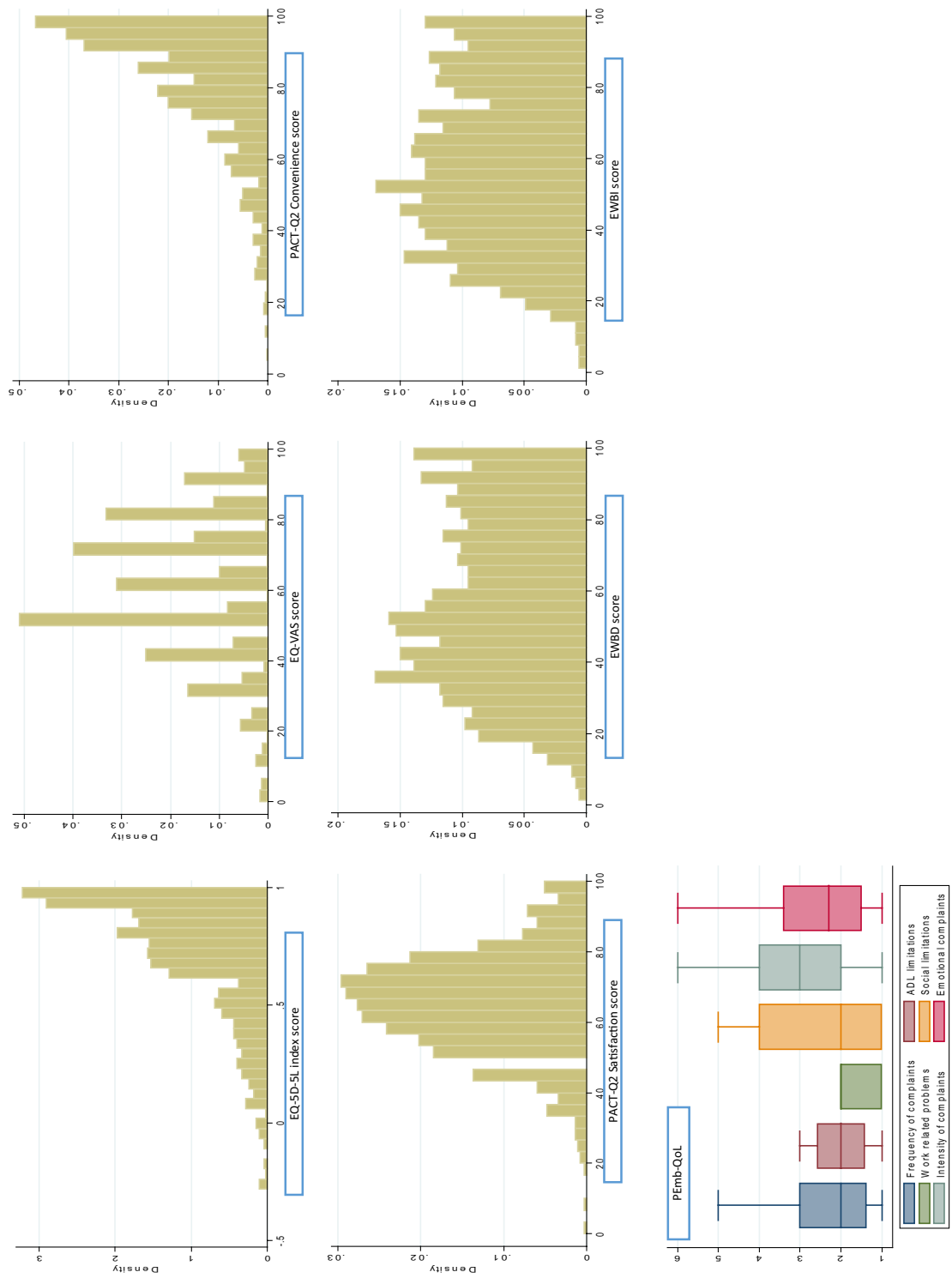

Fig. 1 Distribution of summary score of each questionnaire in PE (total sample)

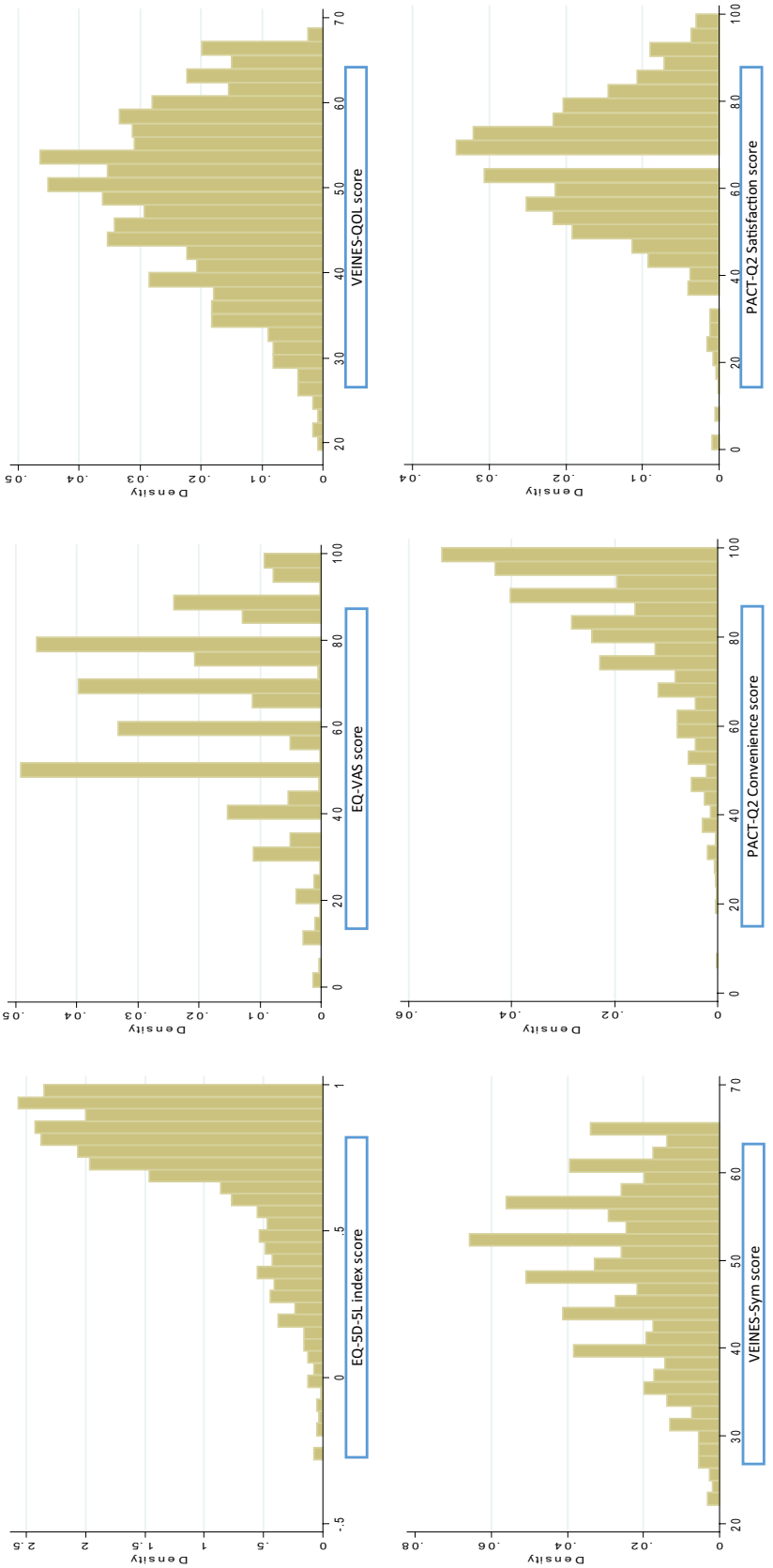

Fig. 2 Distribution of summary score of each questionnaire in DVT (total sample)

Table 3 Convergent validity, correlation between scores of each measure at baseline

Variables	PE								DVT				
	PEmb-QoL							PACT-Q2		VEINES-QOL/Sym		PACT-Q2	
	FO	ADLL	WP	SL	IO	EC	EWBD	EWBI	Convenience	Satisfaction	VEINES-QOL	VEINES-Sym	Convenience	Satisfaction
EQ-5D-5L index score	− 0.173	− 0.475	− 0.215	− 0.247	− 0.165	− 0.391	0.358	0.435	0.348	0.226	0.476	0.336	0.326	0.179
EQ-5D VAS	− 0.209	− 0.443	− 0.271	− 0.245	− 0.218	− 0.378	0.382	0.439	0.257	0.231	0.343	0.221	0.282	0.155

FO frequency of complains, *ADLL* ADL limitations, *WP* work related problems, *SL* social limitations, *IO* Intensity of complains, *EC* emotional complains, EWBD equal weight based on each dimension, *EWBI* equal weight based on each item

comorbidity known-group test in the German and English versions and death known-group test in the English version. For instance, in the comorbidity known group, several domains of PEmb-QoL, including ADL limitations, work-related problems, social limitations and emotional complain, were associated with a larger effect size/relative efficiency in the German version. Similarly, in death known-group test, frequency of complain, ADL limitations, intensity of complain and emotional complain domain of PEmb-QoL, were associated with a larger effect size/relative efficiency in the English version. Similar results were observed in DVT study population—EQ-5D-5L index/VAS score was overall associated with a larger effect size/relative efficiency in the most of comparisons (Table 5 and Table 10 in "Appendix" section). The exceptions included VEINES-QOL/Sym had a better effect size/relative efficiency in distal vs. proximal known group in the French, Spanish and English versions, as well as in comorbidity known group for the German one. PACT-Q2 performed better in death known group for the English and Spanish versions.

Responsiveness

Table 6 and Table 11 in "Appendix" section present the results of responsiveness analysis. In the PE study population, 80 patients reported having any one of the predefined clinical events (see methods) during the 1-month follow up. For those patients who experienced clinical events, the mean changes of examined scores showed minor improvements or worsening, whereas larger improvements were observed in patients without clinical events. The EQ-5D-5L index score was more responsive, having a larger effect size and a larger relative efficiency than EQ-5D VAS, PEmb-QoL and PACT-Q2. However, ADL limitation and emotional complaint domains of PEmb-QoL were associated with larger responsiveness in the French version, and work-related problems and emotional complaint domains in the German version. PACT-Q2 also showed larger responsiveness in French and German samples. Whereas, in the DVT study population, both the EQ-5D-5L index and VAS scores were associated with larger effect size and larger relative efficiency and thus were more responsive than others. However, PACT-Q2 satisfaction score had a better responsiveness in the German and English language samples. Of note, the reader should be aware of the small number of patients in each language sample with clinical events in the follow-up.

Table 4 Known-group validity in PE study population—difference in baseline score between known groups

PE	*n*	EQ-5D-5L		PEmb-QoL					
Grouping variable		Index score	VAS score	FO	ADLL	WP	SL	IO	EC
Provoked									
No	768	0.754 (0.233)	61.68 (19.96)	2.27 (1.03)	1.96 (0.64)	1.60 (0.44)	2.50 (1.33)	3.25 (1.38)	2.49 (1.18)
Yes	286	0.618 (0.301)*	55.93 (21.85)*	2.29 (1.03)	2.12 (0.69)*	1.65 (0.44)	2.67 (1.47)	3.22 (1.44)	2.77 (1.27)*
Mean difference		0.136	5.749	− 0.021	− 0.156	− 0.058	− 0.17	0.036	− 0.282
ES		0.52	0.28	0.02	0.24	0.13	0.12	0.03	0.23
RE		1	0.27	0.00	0.20	0.06	0.05	0.00	0.19
Comorbidity									
≤ 1	518	0.743 (0.243)	63.50 (20.65)	2.28 (1.05)	1.90 (0.66)	1.57 (0.45)	2.48 (1.37)	3.22 (1.46)	2.45 (1.20)
> 1	536	0.692 (0.273)*	56.86 (20.11)*	2.27 (1.01)	2.11 (0.65)*	1.66 (0.42)*	2.61 (1.37)	3.26 (1.33)	2.68 (1.22)*
Mean difference		0.051	6.642	0.01	− 0.209	− 0.097	− 0.131	− 0.04	− 0.234
ES		0.20	0.32	0.01	0.32	0.10	0.10	0.03	0.19
RE		1	2.76	0.00	2.66	1.26	0.24	0.02	0.98
Dead									
Yes	60	0.556 (0.319)	47.58 (20.38)	2.36 (1.04)	2.25 (0.68)	1.70 (0.44)	2.92 (1.48)	3.22 (1.26)	3.00 (1.30)
No	904	0.727 (0.253)*	61.18 (20.32)*	2.26 (1.03)	1.98 (0.66)*	1.60 (0.44)	2.50 (1.36)*	3.24 (1.42)	2.51 (1.17)*
Mean difference		− 0.171	− 13.60	0.105	0.266	0.101	0.417	− 0.018	0.494
ES		0.66	0.66	0.10	0.40	0.23	0.31	0.01	0.42
RE		1	1.01	0.02	0.37	0.12	0.21	0	0.40

PE	*n*	PACT-Q2			
Grouping variable		EWBD	EWBI	Convenience	Satisfaction
Provoked					
No	768	57.96 (23.74)	59.91 (22.62)	82.53 (16.35)	66.45 (14.98)
Yes	286	54.08 (25.45)*	55.08 (24.16)*	76.30 (19.61)*	63.09 (14.33)*
Mean difference		3.880	4.822	6.23	3.37
ES		0.16	0.21	0.36	0.23
RE		0.09	0.15	0.45	0.18
Comorbidity					
≤ 1	518	59.33 (24.88)	61.57 (23.31)	82.17 (16.26)	66.42 (15.04)
> 1	536	54.56 (23.44)*	55.72 (22.62)*	79.55 (18.56)*	64.69 (14.67)
Mean difference		4.77	5.85	2.62	1.74
ES		0.20	0.25	0.15	0.12
RE		1.01	1.68	0.59	0.35
Dead					
Yes	60	50.14 (25.64)	50.39 (25.41)	75.10 (20.32)	62.26 (14.88)
No	904	57.81 (24.02)*	59.56 (22.85)*	80.99 (17.19)*	65.85 (14.83)
Mean difference		− 7.668	− 9.162	− 5.899	− 3.592
ES		0.32	0.40	0.34	0.24
RE		0.23	0.36	0.26	0.13

FO frequency of complains, *ADLL* ADL limitations, *WP* work related problems, *SL* social limitations, *IO* Intensity of complains, *EC* emotional complains, EWBD equal weight based on each dimension, *EWBI* equal weight based on each item, *ES* effect size, *RE* relative efficiency

*p-value ≤ 0.05

Single summary score of PEmb-QoL

The summary score of the six domain scores or all items (based on equal weight from each domain or equal weight from each item), did not reflect the high proportion of patients with maximum (ceiling) or minimum (floor) score (100/0) seen in some original domains. Furthermore, the single summary score of PEmb-QoL based on

Table 5 Known-group validity in DVT study population—difference in baseline score between known groups

Grouping variable	*n*	EQ-5D-5L		VEINES-QOL/Sym		PACT-Q2	
		Index score	VAS score	VEINES-QOL	VEINS-Sym	Convenience	Satisfaction
Provoked							
No	1118	0.748 (0.227)	66.38 (19.74)	49.83 (9.74)	49.50 (9.71)	82.76 (15.97)	65.72 (15.72)
Yes	419	0.638 (0.268)*	60.82 (20.38)*	47.65 (9.61)*	48.68 (9.73)	81.17 (15.57)	64.57 (14.39)
Mean difference		0.106	5.565	2.185	0.816	1.596	1.150
ES		0.44	0.28	0.22	0.08	0.10	0.08
RE		1	0.4	0.26	0.04	0.05	0.03
Distal versus proximal							
Distal	437	0.756 (0.214)	68.03 (19.07)	51.24 (9.72)	51.14 (9.62)	83.94 (14.60)	65.49 (16.18)
Proximal	1100	0.705 (0.252)*	63.61 (20.31)*	48.44 (9.65)*	48.53 (9.66)*	81.69 (16.30)*	65.37 (15.04)
Mean difference		0.051	4.42	2.799	2.611	2.253	0.117
ES		0.21	0.22	0.29	0.27	0.14	0.01
RE		1	1.11	1.89	1.66	0.46	0.00
Comorbidity							
≤ 1	793	0.742 (0.236)	68.05 (20.03)	50.18 (9.88)	50.15 (9.86)	83.25 (14.60)	65.93 (15.39)
> 1	744	0.696 (0.247)*	61.48 (19.55)*	48.24 (9.52)*	48.34 (9.48)*	81.34 (17.05)*	64.84 (15.35)
Mean difference		0.046	6.572	1.935	1.81	1.912	1.096
ES		0.19	0.33	0.2	0.19	0.12	0.07
RE		1	3.00	1.08	0.95	0.40	0.14
Dead							
Yes	94	0.618 (0.260)	49.06 (19.89)	47.82 (10.00)	49.23 (9.70)	76.04 (21.01)	59.92 (12.38)
No	1248	0.739 (0.229)*	66.29 (19.37)*	49.67 (9.51)	49.66 (9.52)	83.05 (15.24)*	66.28 (15.45)*
Mean difference		− 0.121	− 17.23	− 1.85	− 0.426	− 7.011	− 6.364
ES		0.52	0.87	0.19	0.04	0.44	0.41
RE		1	2.87	0.14	0.01	0.73	0.63

ES effect size, *RE* relative efficiency

*p-value ≤ 0.05

items correlated slightly better with the EQ-5D-5L index score than that based on domain (Table 2). In terms of known-group validity and responsiveness analyses, neither summary score outperformed EQ-5D-5L index or the VAS score (except the comorbidity known-group test in the German version). However, the single summary score based on items tended to associate with slightly larger effect size and relative efficiency compared to those based on domains.

Discussion

This study aimed to compare the measurement properties between EQ-5D-5L, disease-specific questionnaires (PEmb-QoL and VEINES-QOL/Sym) and treatment-specific questionnaire (PACT-Q2) in both PE and DVT populations. The results suggest EQ-5D-5L performed better in some psychometric properties among French, Italian and Spanish language versions. Overall, EQ-5D-5L is comparable to PEmb-QoL, VENS-QOL/Sym and PACT-Q2 in terms of acceptability, validity and responsiveness in each language setting.

Disease-specific versus generic quality of life measures

Deep venous thrombosis (PE and/or DVT) impose substantial disease burden, such as pain and suffering, loss of mobility, impairment of function at work and at home, and psychological distress [25]. It is known that 30–50% of patients with VTE might develop post-thrombotic syndrome (PTS), which has a long-term impact on patient's quality of life; similarly post-pulmonary embolism syndrome is associated with a long-term consequence after an acute PE event. Several disease-specific quality of life instruments have been developed to quantify the impact of VTE. Amongst others, PEmb-QoL and VEINES-QOL/Sym are the

Table 6 Responsiveness—score change between 1-month follow-up and baseline

PE	*n*	EQ-5D-5L		PEmb-QoL				
		Index score	VAS score	FO	ADLL	WP	SL	IO
Clinical event								
No	539	0.098 (0.234)	8.13 (18.22)	− 0.280 (0.907)	− 0.252 (0.593)	− 0.034 (0.490)	− 0.299 (1.277)	− 0.683 (1.391)
Yes	80	− 0.007 (0.241)*	6.85 (23.50)	− 0.156 (1.104)	− 0.032 (0.746)*	− 0.013 (0.472)	− 0.188 (1.535)	− 0.594 (1.378)
Mean difference		0.105	1.28	− 0.220	− 0.124	− 0.220	− 0.022	− 0.111
ES		0.442	0.068	0.133	0.356	0.045	0.085	0.064
RE		1	0.023	0.089	0.643	0.010	0.036	0.021

PE	*n*	PEmb-QoL			PACT-Q2	
		EC	EWBD	EWBI	Convenience	Satisfaction
Clinical event						
No	539	0.025 (1.032)	7.281 (21.164)	6.664 (19.518)	1.213 (12.922)	3.512 (15.161)
Yes	80	0.364 (1.045)*	2.676 (24.590)*	0.223 (23.535)*	0.192 (14.612)	− 1.696 (15.541)*
Mean difference		− 0.339	4.605	6.441	1.021	5.208
ES		0.326	0.212	0.319	0.077	0.340
RE		0.541	0.228	0.517	0.030	0.589

DVT	*n*	EQ-5D-5L		VEINES-QOL/Sym		PACT-Q2	
		Index score	VAS score	VEINES-QOL	VEINES-Sym	Convenience	Satisfaction
Clinical event							
No	817	0.069 (0.201)	5.03 (16.70)	0.227 (8.519)	0.640 (8.204)	1.123 (12.771)	3.453 (15.219)
Yes	66	− 0.045 (0.251)*	− 5.15 (19.72)*	− 0.232 (8.787)	− 0.538 (8.679)	− 1.719 (14.245)	− 1.136 (15.664)*
Mean difference		0.114	10.181	0.459	1.179	2.95	4.590
ES		0.55	0.59	0.05	0.14	0.23	0.30
RE		1	1.16	0.07	0.01	0.17	0.29

FO frequency of complains, *ADLL* ADL limitations, *WP* work related problems, *SL* social limitations, *IO* Intensity of complains, *EC* emotional complains, EWBD equal weight based on each dimension, *EWBI* equal weight based on each item, *ES* effect size, *RE* relative efficiency

*p-value ≤ 0.05

most frequently used disease-specific measurements in PE and DVT, respectively. The psychometric properties of each measure have been validated in several studies [18, 19]. Disease-specific measure is generally considered to capture all relevant impact of a given disease on quality of life, so that it is more sensitive to change. However, it does not allow comparison across different diseases. With limited healthcare resources available to society and with the spread of the use of health technology assessment, generic quality of life measurements (particularly generic preference-based quality of life measurements such as EQ-5D), which is suitable for comparative purposes, has grown in importance. While focusing on limited domains of quality of life, a generic measure is usually shorter and easier to complete; since the same items are used to measure each disease, generic measures allow for direct comparison. It is recommended to use both generic and disease-specific measures in clinical trials or observation studies to fully understand the impact of a disease on health-related quality of life as both measures complement each other [26]. Thus, with the current study validating the use of EQ-5D-5L in PE and DVT patients, it facilitates future study in measuring humanistic burden of PE/DVT to use EQ-5D-5L alongside disease-specific measures.

Despite the fact that the current study demonstrates EQ-5D-5L is associated with great effect size/better *F*-statistics in most known-group and responsiveness comparisons, it should be noted that each measure is designed to capture

different aspects of health-related quality of life as discussed above, and therefore there is no better or worse measure and the choice will depend on the purpose of the study.

Summary score of PEmb-QoL

The study explored the possibility of having a single summary score for PEmb-QoL. Due to the fact that PEmb-QoL generates six domain scores and each score is presented in a Likert scale, it makes the comparison with other measures, whose scores presumably possess cardinal property, difficult. To facilitate the comparison, a single summary score, based on either equal weight on each domain or on each item, was calculated. The findings suggested that the single summary score resulted in a favorable effect size compared to most of individual domains, with the summary score based on item performing better than that based on domain. Future development of PEmb-QoL might want to consider developing a set of weight for converting six domains to a single summary score.

Future research

More discordances were observed in the German and English versions compared to others. Potentially, the small PE sample size in these two versions might be one of the causes. Future research might help in understanding this observed difference. As one of the limitations of the current study, due to the use of the complete cases in the analyses, the study assumed that the relationship between instruments observed from the complete cases were the same as those from the unobserved/missing data. Potentially, the issue can be addressed by imputing missing values through one of imputation techniques, such as multiple imputation method, to take into account the missing data. Given the design of the PREFER in VTE registry, test–retest reliability, was not assessed. Test–retest reliability property is an indicator of the stability of an instrument, by administering the instrument to respondents on two different occasions and examining the correlation between test and retest scores. Future study should address this property. The estimation of the value for the minimal (clinically) important difference (MID/MCID) is also desirable. MID/MCID value is used to assist in the decision that whether the observed improvement/worse (change) in health-related quality of life score is clinically relevant or not. Such value helps bridging the link between patient-reported outcome and clinical decision-making.

Conclusion

The EQ-5D-5L is a valid and responsive questionnaire to be used in pulmonary embolism and deep vein thrombosis populations in the French, German, Italian, Spanish and English language settings. EQ-5D-5L performed better in some psychometric properties among French, Italian and Spanish language versions. EQ-5D-5L demonstrates its comparability in measurement properties in comparison to PEmb-QoL, VEINES-QOL/Sym and PACT-Q2 disease/treatment-specific questionnaires.

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Compliance with ethical standards

Conflict of interest L.H. Chuang, S. Kroep, and B. van Hout have served as consultants for Daiichi-Sankyo; A. Cohen, M. Monreal, S. Willich, A. Gitt, R. Bauersachs and G. Agnelli have received honoraria from Daiichi-Sankyo for participating in the advisory committee; P Gumbs is an employee of Daiichi-Sankyo Europe GmbH.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Appendix

See Tables 7, 8, 9, 10 and 11.

Table 7 Acceptability by each language version—scores of each measure at baseline

Disease	Measures	Scores	French ($n=296$)					Germen ($n=170$)				
			Mean (SD)	Median	% "floor"	% "ceiling"	Missing[a]	Mean (SD)	Median	% "floor"	% "ceiling"	Missing[a]
PE	EQ-5D-5L	Index score	0.703 (0.264)	0.772	0	14.19	2.84	0.755 (0.242)	0.816	0	15.88	3.73
		VAS	60.22 (20.36)	60	0.68	0.68		62.06 (19.65)	62.5	0	0.59	
	PEmb-QoL	Frequency of complains	2.24 (1.07)	2	12.50	1.69	6.82	2.37 (1.01)	2.25	8.82	0.59	7.47
		ADL limitations	1.97 (0.66)	2	9.80	7.77		1.93 (0.62)	1.92	12.94	2.94	
		Work related problems	1.56 (0.46)	1.75	35.14	46.96		1.55 (0.44)	1.75	33.53	38.24	
		Social limitations	2.42 (1.38)	2	35.88	8.78		2.54 (1.5)	2	35.88	17.06	
		Intensity of complains	3.36 (1.53)	3.5	15.20	4.73		3.24 (1.5)	3	13.53	6.47	
		Emotional complains	2.43 (1.19)	2.2	11.15	0.68		2.29 (1.1)	2.1	11.18	0.00	
		EWBD	58.9 (24.52)	57.22	0	2.03		59.27 (25)	59.82	0	1.76	
		EWBI	60.56 (22.97)	59.93	0.34	2.03		61.58 (22.33)	62.76	0	1.76	
	PACT-Q2	Convenience	85.21 (13.38)	88.46	0	8.78	9.66	84.69 (15.22)	90.38	0	11.76	23.65
		Treatment satisfaction	68.4 (14.64)	71.43	0	2.36		61.97 (16.11)	60.71	0.59	1.76	
Disease	Measures	Scores	French ($n=172$)					German ($n=482$)				
			Mean (SD)	Median	% "floor"	% "ceiling"	Missing[a]	Mean (SD)	Median	% "floor"	% "ceiling"	Missing[a]
DVT	EQ-5D-5L	Index score	0.728 (0.26)	0.813	0.58	15.70	3.78	0.764 (0.209)	0.817	0.21	11.83	3.85
		VAS	67.8 (20.65)	70	0.58	4.07		65.87 (18.81)	70	0.21	1.24	
	VEINES-QOL/Sym	VEINES-QOL	52.45 (10.05)	53.79	–	–	11.34	51.23 (8.52)	52.25	–	–	7.87
		VEINES-Sym	51.78 (10.07)	52.96	–	–		50.94 (8.78)	51.90	–	–	
	PACT-Q2	Convenience	87.87 (11.35)	90.38	0	11.05	18.91	87.06 (13.44)	90.38	0	14.94	16.05
		Treatment satisfaction	68.21 (15.58)	69.64	0.58	1.74		66.35 (16.69)	67.86	0.41	0.83	
Disease	Measures	Scores	Italian ($n=252$)					Spanish ($n=219$)				
			Mean (SD)	Median	% "floor"	% "ceiling"	Missing[a]	Mean (SD)	Median	% "floor"	% "ceiling"	Missing[a]
PE	EQ-5D-5L	Index score	0.651 (0.295)	0.716	1.19	7.94	2.11	0.774 (0.226)	0.828	0.91	19.63	1.83
		VAS	57.61 (21.1)	60	0.40	1.59		60.48 (20.89)	60	0.46	3.20	
	PEmb-QoL	Frequency of complains	2.14 (0.91)	1.88	7.14	1.59	4.52	2.25 (1.04)	2	12.33	0.46	5.2
		ADL limitations	2.17 (0.67)	2.25	7.14	14.29		1.89 (0.66)	1.92	15.53	4.11	
		Work related problems	1.68 (0.43)	2	24.21	57.94		1.61 (0.45)	2	30.14	50.23	
		Social limitations	2.69 (1.32)	3	26.98	9.92		2.37 (1.28)	2	37.44	2.74	
		Intensity of complains	3.16 (1.27)	3	9.13	0.79		3.04 (1.27)	3	11.42	2.28	
		Emotional complains	2.88 (1.27)	2.7	6.75	0.79		2.47 (1.11)	2.3	10.50	0.00	
		EWBD	53.6 (23.79)	49.55	0	1.98		59.8 (23.75)	55.52	0	2.28	
		EWBI	54.09 (23.47)	52.03	0	1.98		61.63 (23)	59.61	0	2.28	
	PACT-Q2	Convenience	68.46 (20.66)	73.08	0	1.98	20.18	82.19 (16.23)	86.54	0	8.68	29.36
		Treatment satisfaction	60.63 (13.16)	60.71	0	0.40		68.38 (14.5)	67.86	0	2.74	

Table 7 (continued)

Disease	Measures	Scores	Italian ($n=433$)					Spanish ($n=151$)				
			Mean (SD)	Median	% "floor"	% "ceiling"	Missing[a]	Mean (SD)	Median	% "floor"	% "ceiling"	Missing[a]
DVT	EQ-5D-5L	Index score	0.688 (0.256)	0.761	0.00	7.39	3.13	0.71 (0.238)	0.792	0	7.28	0.81
		VAS	62.03 (21.36)	65	1.15	2.77		63.52 (20.1)	70	0	3.31	
	VEINES-QOL/Sym	VEINES-QOL	48.91 (9.51)	49.24	–	–	6.26	48.18 (8.3)	48.04	–	–	4.07
		VEINES-Sym	50 (9.25)	50.84	–	–		47.06 (8.76)	47.65	–	–	
	PACT-Q2	Convenience	74.5 (17.77)	76.92	0	5.31	17.22	81.46 (13.54)	82.69	0	3.97	33.33
		Treatment satisfaction	62.52 (13.33)	64.29	0.46	0.46		66.37 (13.28)	64.29	0	1.32	

Disease	Measures	Scores	English ($n=117$)				
			Mean (SD)	Median	% "floor"	% "ceiling"	Missing[a]
PE	EQ-5D-5L	Index score	0.734 (0.221)	0.770	0	11.11	0.68
		VAS	61.79 (21.06)	60	0.85	5.13	
	PEmb-QoL	Frequency of complains	2.53 (1.1)	2.375	2.56	2.56	4.76
		ADL limitations	2.08 (0.62)	2.08	5.98	7.69	
		Work related problems	1.73 (0.39)	2	16.24	60.68	
		Social limitations	2.92 (1.37)	3	21.37	13.68	
		Intensity of complains	3.51 (1.34)	3.5	5.13	8.55	
		Emotional complains	2.8 (1.31)	2.6	5.98	0	
		EWBD	50.13 (22.71)	49.18	0.85	0	
		EWBI	53.34 (22.21)	53.29	0	0	
	PACT-Q2	Convenience	88.31 (10.4)	90.38	0	12.82	12.24
		Treatment satisfaction	68.74 (14.06)	71.43	0	0.85	

Disease	Measures	Scores	English ($n=299$)				
			Mean (SD)	Median	% "floor"	% "ceiling"	Missing[a]
DVT	EQ-5D-5L	Index score	0.694 (0.254)	0.761	0.33	7.36	1.6
		VAS	66.34 (19.3)	70	0	2.68	
	VEINES-QOL/Sym	VEINES-QOL	45.19 (10.92)	46.24	–	–	3.21
		VEINES-Sym	45.22 (10.66)	45.52	–	–	
	PACT-Q2	Convenience	83.3 (15.4)	86.54	0	6.35	13.64
		Treatment satisfaction	65.95 (16.23)	67.86	0	1.34	

EWBD equal weight based on each dimension, *EWBI* equal weight based on each item

[a]EQ-5D-5L: missing any of six items (including EQ-VAS); VEINES-QOL/Sym: more than 12 items (out of 25) missing; PEmb-QoL: 50% missing at any of six dimensions; PACT-Q2: more than 7 + 5 items missing

Table 8 Convergent validity, correlation between scores of each measure at baseline

PE	PEmb-QoL								PACT-Q2		VEINES-QOL/Sym		PACT-Q2	
	FO	ADLL	WP	SL	IO	EC	EWBD	EWBI	Convenience	Satisfaction	VEINES-QOL	VEINES-Sym	Convenience	Satisfaction
French														
EQ-5D-5L index score	− 0.213	− 0.509	− 0.201	− 0.256	− 0.252	− 0.290	0.375	0.442	0.234	0.143	0.416	0.272	0.166	0.106
EQ-5D VAS	− 0.252	− 0.462	− 0.280	− 0.256	− 0.279	− 0.343	0.410	0.464	0.216	0.242	0.211	0.144	0.274	0.148
German														
EQ-5D-5L index score	− 0.071	− 0.374	− 0.178	− 0.275	− 0.115	− 0.440	0.298	0.358	0.294	0.158	0.434	0.289	0.285	0.068
EQ-5D VAS	− 0.193	− 0.443	− 0.172	− 0.272	− 0.211	− 0.407	0.344	0.417	0.202	0.180	0.377	0.268	0.239	0.020
Italian														
EQ-5D-5L index score	− 0.217	− 0.513	− 0.258	− 0.258	− 0.145	− 0.425	0.393	0.478	0.407	0.317	0.448	0.325	0.285	0.165
EQ-5D VAS	− 0.229	− 0.426	− 0.309	− 0.268	− 0.217	− 0.387	0.398	0.444	0.356	0.238	0.29	0.17	0.22	0.12
Spanish														
EQ-5D-5L index score	− 0.126	− 0.311	− 0.134	− 0.135	− 0.015	− 0.379	0.229	0.303	0.395	0.232	0.363	0.127	0.326	0.154
EQ-5D VAS	− 0.169	− 0.420	− 0.279	− 0.201	− 0.129	− 0.362	0.340	0.398	0.195	0.282	0.363	0.127	0.326	0.154
English														
EQ-5D-5L index score	− 0.349	− 0.629	− 0.341	− 0.328	− 0.299	− 0.458	0.539	0.616	0.220	0.247	0.613	0.499	0.451	0.375
EQ-5D VAS	− 0.242	− 0.466	− 0.282	− 0.223	− 0.270	− 0.416	0.423	0.473	0.244	0.168	0.501	0.372	0.387	0.327

FO frequency of complains, *ADLL* ADL limitations, *WP* work related problems, *SL* social limitations, *IO* Intensity of complains, *EC* emotional complains, EWBD equal weight based on each dimension, *EWBI* equal weight based on each item

Table 9 Known-group validity in PE study population—difference in baseline score between known groups

	Index score	VAS score	FO	ADLL	WP	SL	IO	EC	EWBD	EWBI	Convenience	Satisfaction
French												
Provoked												
Mean difference	0.077	1.186	0.106	− 0.011	0.011	0.058	0.317	0.169	− 2.386	− 1.792	1.674	3.518
ES	0.29	0.06	0.10	0.02	0.02	0.04	0.21	0.14	0.10	0.08	0.13	0.24
RE	1	0.04	0.11	0.00	0.01	0.02	0.50	0.23	0.11	0.07	0.18	0.67
Comorbidity > 1												
Mean difference	0.018	5.783	0.002	− 0.143	− 0.101	− 0.108	− 0.175	− 0.263	4.772	4.960	0.354	2.020
ES	0.07	0.28	0.00	0.22	0.22	0.08	0.11	0.22	0.19	0.22	0.03	0.14
RE	1	17.23	0.00	9.89	10.23	1.29	2.77	10.26	8.00	9.86	0.14	4.00
Death												
Mean difference	− 0.106	− 14.581	0.057	0.077	0.027	0.096	− 0.199	0.261	− 1.939	− 3.270	− 1.838	− 0.696
ES	0.40	0.73	0.05	0.12	0.06	0.07	0.13	0.22	0.08	0.14	0.14	0.05
RE	1	3.34	0.02	0.08	0.02	0.03	0.10	0.31	0.04	0.12	0.11	0.02
German												
Provoked												
Mean difference	0.171	6.289	− 0.158	− 0.264	− 0.201	− 0.902	− 0.397	− 0.804	13.978	12.534	6.100	2.006
ES	0.71	0.32	0.16	0.43	0.46	0.60	0.26	0.73	0.56	0.56	0.40	0.12
RE	1	0.19	0.04	0.34	0.40	0.70	0.13	1.08	0.60	0.61	0.30	0.03
Comorbidity > 1												
Mean difference	0.018	2.536	0.063	− 0.235	− 0.088	− 0.338	0.079	− 0.125	4.717	5.343	− 0.856	0.552
ES	0.08	0.13	0.06	0.38	0.20	0.22	0.05	0.11	0.19	0.24	0.06	0.03
RE	1	2.92	0.67	25.88	7.17	8.96	0.50	2.25	6.29	10.17	0.54	0.21
Death												
Mean difference	− 0.091	− 2.138	− 0.733	− 0.487	− 0.539	0.467	− 0.214	2.124	7.786	5.560	− 8.047	− 15.813
ES	na	na	na	na	na	na	na	na	na	na	na	na
RE	na	na	na	na	na	na	na	na	na	na	na	na
Italian												
Provoked												
Mean difference	0.202	11.794	− 0.186	− 0.272	− 0.068	− 0.330	− 0.173	− 0.357	7.318	8.458	6.700	3.500
ES	0.68	0.56	0.20	0.40	0.16	0.25	0.14	0.28	0.31	0.36	0.32	0.27
RE	1	0.64	0.08	0.32	0.05	0.12	0.04	0.15	0.18	0.25	0.21	0.14
Comorbidity > 1												
Mean difference	0.106	10.769	− 0.149	− 0.302	− 0.123	− 0.106	− 0.208	− 0.267	7.213	9.072	1.927	1.186
ES	0.36	0.51	0.16	0.45	0.29	0.08	0.16	0.21	0.30	0.39	0.09	0.09
RE	1	2.06	0.20	1.58	0.63	0.05	0.20	0.33	0.70	1.15	0.06	0.06
Death												
Mean difference	− 0.247	− 17.587	0.298	0.298	0.120	0.600	0.355	0.624	− 11.492	− 12.133	− 4.378	− 5.913

Table 9 (continued)

	Index score	VAS score	FO	ADLL	WP	SL	IO	EC	EWBD	EWBI	Convenience	Satisfaction
ES	0.85	0.84	0.33	0.45	0.29	0.46	0.28	0.50	0.50	0.53	0.21	0.45
RE	1	0.98	0.14	0.26	0.11	0.28	0.10	0.33	0.32	0.36	0.06	0.26
Spanish												
Provoked												
Mean difference	0.097	3.936	0.143	0.010	− 0.028	0.227	0.307	− 0.327	− 1.087	0.596	4.866	0.429
ES	0.43	0.19	0.14	0.02	0.06	0.18	0.24	0.29	0.05	0.03	0.30	0.03
RE	1	0.19	0.10	0.00	0.02	0.16	0.31	0.45	0.01	0.00	0.47	0.01
Comorbidity > 1												
Mean difference	0.041	5.467	− 0.064	− 0.088	− 0.088	− 0.138	− 0.047	− 0.194	3.834	3.952	0.312	1.878
ES	0.18	0.26	0.06	0.13	0.20	0.11	0.04	0.17	0.16	0.17	0.02	0.13
RE	1	2.05	0.11	0.52	1.15	0.35	0.04	0.90	0.77	0.88	0.01	0.50
Death												
Mean difference	− 0.020	− 7.529	0.266	0.135	0.092	0.274	− 0.140	0.092	− 4.759	− 5.424	5.803	2.466
ES	0.08	0.35	0.25	0.21	0.21	0.21	0.11	0.09	0.20	0.24	0.36	0.17
RE	1	17.50	9.00	5.90	5.90	6.40	1.60	1.00	5.50	7.70	17.90	4.10
English												
Provoked												
Mean difference	0.046	− 0.074	− 0.223	− 0.133	0.044	0.189	− 0.128	0.089	0.636	2.189	0.086	2.870
ES	0.21	0.00	0.20	0.21	0.12	0.14	0.10	0.07	0.03	0.10	0.01	0.20
RE	1	0.00	0.93	1.05	0.31	0.43	0.21	0.10	0.02	0.22	0.00	0.95
Comorbidity > 1												
Mean difference	0.006	6.208	0.175	− 0.187	0.013	0.208	0.265	0.100	− 1.482	0.969	− 0.666	− 3.599
ES	0.03	0.29	0.16	0.30	0.03	0.15	0.20	0.08	0.07	0.04	0.06	0.26
RE	1	127.00	36.50	134.00	2.00	33.00	56.50	8.50	6.00	2.50	6.00	95.50
Death												
Mean difference	− 0.169	17.934	− 1.228	0.801	− 0.195	0.220	− 1.956	− 1.286	11.585	4.029	− 1.437	5.573
ES	0.73	0.86	1.09	1.28	0.49	0.16	1.42	1.03	0.52	0.18	0.13	0.40
RE	1	1.37	2.24	3.12	0.45	0.05	3.88	1.99	0.50	0.06	0.03	0.30

Due to the fact that there is only one observation in one of the two comparison groups

ES effect size, *RE* relative efficiency, *FO* frequency of complains, *ADLL* ADL limitations, *WP* work related problems, *SL* social limitations, *IO* Intensity of complains, *EC* emotional complains, EWBD equal weight based on each dimension, *EWBI* equal weight based on each item, *na* not available

Table 10 Known-group validity in DVT study population—difference in baseline score between known groups

	Index score	VAS score	VEINES-QOL	VEINES-Sym	Convenience	Satisfaction
French						
Provoked						
Mean difference	0.180	4.438	4.707	2.049	1.964	1.892
ES	0.69	0.21	0.47	0.20	0.17	0.12
RE	1	0.09	0.44	0.08	0.06	0.03
Proximal						
Mean difference	0.022	3.499	3.248	3.158	− 1.248	− 2.468
ES	0.08	0.17	0.32	0.31	0.11	0.16
RE	1	4.13	15.27	14.37	1.73	3.60
Comorbidity > 1						
Mean difference	0.059	10.029	0.811	1.052	-2.267	2.409
ES	0.23	0.49	0.08	0.10	0.20	0.15
RE	1	4.84	0.13	0.21	0.78	0.46
Death						
Mean difference	− 0.021	− 22.314	2.129	2.937	1.841	− 9.084
ES	0.09	1.08	0.21	0.29	0.17	0.56
RE	1	162.00	5.75	10.75	3.75	40.50
German						
Provoked						
Mean difference	0.056	2.349	2.451	0.669	0.504	1.161
ES	0.27	0.12	0.29	0.08	0.04	0.07
RE	1	0.22	1.16	0.08	0.02	0.07
Proximal						
Mean difference	0.027	1.858	0.377	− 0.230	0.686	0.044
ES	0.13	0.10	0.04	0.03	0.05	0.00
RE	1	0.61	0.12	0.04	0.16	0.00
Comorbidity > 1						
Mean difference	0.019	6.043	3.338	3.780	− 0.787	− 1.013
ES	0.09	0.32	0.39	0.43	0.06	0.06
RE	1	12.91	19.43	23.65	0.41	0.45
Death						
Mean difference	− 0.065	− 10.159	0.844	− 0.282	− 2.223	− 4.387
ES	0.31	0.54	0.10	0.03	0.17	0.26
RE	1	3.04	0.10	0.01	0.30	0.70
Italian						
Provoked						
Mean difference	0.150	7.789	1.903	1.122	0.639	0.030
ES	0.58	0.36	0.20	0.12	0.04	0.00
RE	1	0.37	0.11	0.04	0.00	0.00
Proximal						
Mean difference	0.063	7.092	2.502	2.946	1.507	− 1.360
ES	0.25	0.33	0.26	0.32	0.08	0.10
RE	1	1.82	1.14	1.68	0.12	0.17
Comorbidity > 1						
Mean difference	0.058	7.972	2.483	2.362	3.788	2.698
ES	0.23	0.37	0.26	0.26	0.21	0.20
RE	1	2.77	1.33	1.28	0.88	0.80
Death						
Mean difference	− 0.154	− 20.017	− 3.417	− 1.666	− 5.149	− 3.776
ES	0.63	0.96	0.37	0.18	0.29	0.29

Table 10 (continued)

	Index score	VAS score	VEINES-QOL	VEINES-Sym	Convenience	Satisfaction
RE	1	2.49	0.33	0.08	0.20	0.21
Spanish						
Provoked						
Mean difference	0.070	7.180	− 0.144	− 0.503	1.460	0.645
ES	0.30	0.36	0.02	0.06	0.11	0.05
RE	1	1.47	0.00	0.04	0.13	0.03
Proximal						
Mean difference	0.019	1.204	0.520	0.918	− 0.498	− 0.536
ES	0.08	0.06	0.06	0.10	0.04	0.04
RE	1	0.58	0.58	1.75	0.25	0.25
Comorbidity > 1						
Mean difference	0.018	5.936	− 0.614	− 1.313	0.344	− 1.016
ES	0.08	0.30	0.07	0.15	0.03	0.08
RE	1	15.76	0.95	4.00	0.10	1.05
Death						
Mean difference	0.030	− 2.508	0.192	0.604	7.110	− 1.082
ES	0.13	0.12	0.02	0.07	0.52	0.08
RE	1	1.00	0.06	0.31	17.50	0.44
English						
Provoked						
Mean difference	0.074	5.254	2.197	1.169	0.517	1.386
ES	0.29	0.27	0.20	0.11	0.03	0.09
RE	1	0.87	0.47	0.14	0.01	0.08
Proximal						
Mean difference	0.074	5.334	3.724	3.907	0.737	1.592
ES	0.29	0.28	0.34	0.37	0.05	0.10
RE	1	0.89	1.37	1.58	0.03	0.11
Comorbidity > 1						
Mean difference	0.041	1.521	0.278	0.182	− 2.138	− 0.173
ES	0.16	0.08	0.03	0.02	0.14	0.01
RE	1	0.24	0.03	0.01	0.74	0.01
Death						
Mean difference	− 0.183	− 12.017	− 1.730	− 1.451	− 12.253	− 12.928
ES	0.75	0.63	0.16	0.14	0.83	0.83
RE	1	0.71	0.04	0.03	1.23	1.22

ES effect Size, *RE* relative efficiency

Table 11 Responsiveness—score change between 1-month follow-up and baseline

PE	Index score	VAS score	FO	ADLL	WP	SL	IO	EC	EWBD	EWBI	Convenience	Satisfaction
French												
Mean difference	0.118	0.973	− 0.099	− 0.309	− 0.013	0.049	− 0.013	− 0.597	5.030	8.986	2.451	7.510
ES	0.43	0.05	0.10	0.48	0.02	0.03	0.01	0.59	0.24	0.46	0.21	0.45
RE	1	0.01	0.05	1.25	0.00	0.00	0.00	1.92	0.30	1.15	0.23	1.09
German												
Mean difference	0.071	− 0.538	− 0.218	− 0.032	0.180	− 0.008	− 0.167	0.287	− 2.195	− 1.941	− 5.682	− 1.786
ES	0.31	0.04	0.24	0.06	0.36	0.01	0.10	0.32	0.10	0.11	0.47	0.11
RE	1	0.01	0.58	0.04	1.35	0.00	0.11	1.05	0.10	0.11	2.36	0.13
Italian												
Mean difference	0.141	5.019	0.032	− 0.060	0.020	− 0.060	0.345	− 0.177	− 0.272	1.006	− 0.421	4.259
ES	0.59	0.27	0.04	0.10	0.04	0.05	0.28	0.16	0.01	0.05	0.03	0.32
RE	1	0.21	0.00	0.03	0.01	0.01	0.21	0.07	0.00	0.01	0.00	0.29
Spanish												
Mean difference	0.167	8.091	− 0.367	− 0.593	− 0.300	− 0.830	− 0.607	− 0.921	20.019	21.447	8.155	11.306
ES	0.88	0.47	0.41	0.87	0.60	0.62	0.47	0.87	0.88	0.95	0.56	0.80
RE	1	0.27	0.20	0.97	0.45	0.48	0.27	0.97	1.00	1.18	0.38	0.82
English												
Mean difference	− 0.118	− 18.912	− 0.181	− 0.194	− 0.093	0.153	− 0.711	− 0.095	5.981	6.145	1.374	3.595
ES	− 0.86	0.97	0.18	0.35	0.20	0.14	0.43	0.09	0.27	0.30	0.16	0.21
RE	1	1.31	0.04	0.15	0.05	0.02	0.23	0.01	0.09	0.11	0.03	0.05

DVT	Index score	VAS score	VEINES-QOL	VEINES-Sym	Convenience	Satisfaction
French						
Mean difference	0.132	11.740	0.894	1.889	1.823	3.061
ES	0.63	0.77	0.10	0.22	0.19	0.16
RE	1	1.51	0.12	0.02	0.09	0.06
German						
Mean difference	0.046	6.289	− 1.991	− 2.114	− 1.149	6.353
ES	0.24	0.38	0.25	0.27	0.10	0.39
RE	1	2.55	1.31	1.14	0.16	2.78
Italian						
Mean difference	0.230	14.280	3.198	4.856	6.529	4.754
ES	1.05	0.79	0.39	0.58	0.46	0.37
RE	1	0.55	0.28	0.13	0.18	0.11
Spanish						
Mean difference	0.145	14.057	− 1.393	− 1.026	3.248	− 5.737
ES	0.62	0.77	0.12	0.10	0.18	0.35

Table 11 (continued)

DVT	Index score	VAS score	VEINES-QOL	VEINES-Sym	Convenience	Satisfaction
RE	1	1.58	0.03	0.03	0.08	0.31
English						
Mean difference	− 0.062	1.484	− 1.457	− 1.975	1.534	8.560
ES	0.33	0.09	0.18	− 0.26	0.15	0.55
RE	1	0.08	0.65	0.30	0.20	2.91

ES effect size, *RE* relative efficiency, *FO* frequency of complains, *ADLL* ADL limitations, *WP* work related problems, *SL* social limitations, *IO* Intensity of complains, *EC* emotional complains, EWBD equal weight based on each dimension, *EWBI* equal weight based on each item

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